**TITLE: Effect of Restricted Fluid Management Strategy on Outcomes in Critically Ill Pediatric Trauma Patients: A Multicenter Randomized Controlled Trial**

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## A) ABSTRACT:

**Background:** Aggressive fluid resuscitation has been the cornerstone of early post-operative and trauma management for decades. However, recent prospective adult studies have challenged this practice, linking high volume crystalloid resuscitation to increased mortality, cardiopulmonary, gastrointestinal and hematologic complications. A retrospective study we recently performed at our quaternary-care children's hospital echoed these results. High quality prospective data is necessary to determine best practice guidelines in our pediatric trauma patients.
**Methods:** Currently, no standard exists for the management of crystalloid fluids in critically ill pediatric trauma patients. We propose the first multicenter randomized controlled trial (RCT) comparing a liberal fluid management strategy to a restricted fluid management strategy in critically ill post-operative and trauma patients admitted to the pediatric intensive care unit (ICU). Patients at ten participating centers will be randomized to one of two groups – liberal group or restricted group – each following the same evidence-based physiologic parameters to guide fluid management but differing in the fluid response to these clinical parameters. Our primary outcome will be overall incidence of complications, including major complications – pulmonary edema, hemorrhage, deep cavity infection, anastomotic dehiscence, thrombosis, death, and minor complications – superficial wound infection, ileus, pneumonia. Our secondary outcomes will include need for respiratory support as measured by days on supplemental oxygen and days on the ventilator, ICU length of stay, overall hospital length of stay, and individual complications. **Results:** We anticipate that the restricted fluid arm will have improved outcomes. We predict that these patients will have fewer major and minor complications, decreased oxygen and ventilator requirements, and decreased ICU and overall hospital length of stay.
**Conclusions:** Once we demonstrate that a restricted fluid management strategy significantly improves outcomes, we plan to implement this fluid algorithm in pediatric centers throughout the country.

## B) SPECIFIC AIMS:

We hypothesize that a restricted fluid management strategy will improve clinical outcomes in critically ill pediatric trauma patients when compared to a liberal fluid management strategy. Our specific aims are to demonstrate:
1. The restricted fluid strategy will decrease the overall rate of complications in pediatric trauma patients prior to discharge from the hospital.
2. The restricted fluid strategy will improve pulmonary outcomes - specifically it will decrease the length of respiratory support in these critically ill patients, and that it will decrease ICU and overall hospital lengths of stay.
3. The proposed evidence-based "Restricted Fluid Algorithm" is feasible to implement and adhere to by healthcare practitioners caring for critically ill pediatric surgery and trauma patients in pediatric ICUs of all levels of care.

## C) STUDY PURPOSE AND RATIONAL

**Importance of Problem:** Postoperative patients and trauma patients share the same systemic inflammatory process and capillary leak syndrome that has been traditionally thought to require aggressive fluid resuscitation. As such, crystalloid fluid administration is the cornerstone of treatment of all critically ill pediatric post-operative and trauma patients. Yet, despite significant advances in other aspects of surgical and trauma care, little emphasis has been placed on describing the optimal fluid management strategy in children. As such, no standard exists to guide management of fluids in these patients, even though fluids are intrinsically involved in practically all aspects of their care. While aggressive fluid resuscitation has been a key element of early post-operative and trauma management for decades, recent randomized control trials in adult medical, surgical and trauma patients have demonstrated that liberal crystalloid administration may be associated with adverse clinical outcomes (1-3). Multiple studies in surgical, neurosurgical, burn, and trauma patients have demonstrated that restricting fluids may decrease incidence of death and complications, including – cardiopulmonary complications, Acute Respiratory Distress Syndrome, Multi Organ Failure, abdominal compartment syndrome, surgical site infections, bloodstream infections and gastrointestinal complications (4-9).Small retrospective

studies have shown similar results in critically ill pediatric patients, however data is lacking in pediatric post-operative and trauma patients (10, 11).Most recently, we performed a retrospective study analyzing the effect of aggressive fluid resuscitation on 200 pediatric trauma patients presenting to our Level 1 pediatric trauma center from January 2013 to December 2015. We found that patients who received greater than 60ml/kg/day over the first 48 hours of their hospitalization had increased ventilator use, ICU length of stay, overall length of stay, and time to resumption of a regular diet, even when controlling for GCS, ISS, age, and weight (12). This body of evidence supports the implementation of a prospective trial studying the effects of a restricted fluid strategy in critically ill pediatric trauma patients. We hypothesize that patients undergoing a restricted fluid management strategy will have decreased complications and improved outcomes and quality of life.

**Improvement in Clinical Practice of Pediatric Trauma:** As the evidence is lacking in children, different fluid strategies are currently in practice. Some practitioners provide fluids liberally stating that critically ill post-operative and trauma patients experience a severe inflammatory response that causes a capillary leak syndrome in which fluid leaks out of the capillary system into surrounding tissues. As such, these patients require large volume fluid resuscitation to maintain intravascular volume and remain hemodynamically stable. Conversely, others use a restricted fluid management strategy arguing that such high volumes of fluids worsen acidosis, create local endothelial disruption, and contribute to volume overload from this leaked plasma (13-17). This in turn leads to increased cardiac and pulmonary complications, wound complications, disturbance of the coagulation system and delay in gastrointestinal function. Therefore, we propose a high quality, multicenter, randomized controlled trial, which will compare a liberal fluid management strategy to a restricted fluid management strategy in critically ill pediatric trauma patients. We will determine which fluid strategy leads to improvement in outcomes, including survival and length of hospital stay, and decrease in complications, including cardiac, pulmonary, hematologic, infectious, and gastrointestinal complications.

**Change in Pediatric Surgery and Trauma Management:** We anticipate that if the proposed aims are achieved, we will demonstrate that a restricted fluid management strategy improves outcomes in critically ill pediatric trauma patients. As such, a new evidence-based standard of care will be established for the management of crystalloid fluids in these patients. Instead of following decades old aggressive fluid management strategies, practitioners will tailor their fluid strategy to pre-determined physiologic datapoints and more effectively return their patients to euvolemia as soon as possible.

**Improvement in Health Outcomes of Post-operative and Injured Children and Families and Study Impact on General Good of US Society:** Results from the proposed research will help improve care of the sickest pediatric surgery and trauma patients throughout the country. By demonstrating which fluid management strategy is optimal and most effectively decreases complications and improves outcomes in critically ill pediatric patients, we will have the evidence required to implement this management strategy in pediatric ICUs of all levels of care. We will be able to train physicians and other healthcare practitioners caring for these critically ill children how to use this algorithm to improve outcomes. Through its simplicity and ease of implementation, this management strategy will be passed on to providers in smaller or more rural hospitals to become the new standard of care of pediatric post-operative and trauma patients.
Once the optimal fluid strategy has been demonstrated and implemented throughout hospital systems, outcomes of post-operative and injured children throughout the country will be greatly improved. We anticipate that they will have overall decrease in complications. They will have decrease incidence of pulmonary edema and Acute Respiratory Distress Syndrome, and decreased days on the ventilator or need for oxygen support, which will lead to decreased incidence of pneumonia, lung injury, chronic oxygen use, and tracheostomy. They will have decreased infections leading to decreased need for repeated surgical intervention and decreased pain. They will have fewer coagulopathic complications leading to decreased bleeding and blood clots. The number of days they spend in the ICU and hospital will decrease and they will get home sooner. Their parents will be able to return to work sooner. Overall, their Disability Adjusted Life Years lost from undergoing surgery or having suffered from trauma will be greatly improved (18). This will have a huge impact on the financial health of the patients and their families whose employment will be more secure as they take fewer days off to care for the sick child. Finally, hospital costs will be greatly reduced. We are confident that the impact of this study will be vast and will be felt by all entities linked these patients – their family, the family's employers and the hospital where they receive care.

**(D) STUDY DESIGN AND STATISTICAL ANALYSES**

**Shift in Current Clinical Practice Paradigm:** Currently there is no consensus on which fluid management strategy is optimal in pediatric post-operative and trauma patients. There is emerging data however that administering high volumes of crystalloid fluids is associated with adverse outcomes and increases morbidity. During the resuscitation of a critically ill post-operative or injured child, a branching point at which fluid management may be targeted and reliably protocolized is upon admission to the Intensive Care Unit (ICU), where practitioners are accustomed to the use and analysis of protocolized care to manage their sickest patients. We seek to shift current practice of continued aggressive fluid resuscitation to a more restricted approach that closely follows physiologic indicators of intravascular volume status once patients arrive in the ICU.

**Novel Approach and Refined Intervention:** Liberal and restricted fluid management algorithms are being proposed for critically ill pediatric trauma patients. These algorithms are based on multiple adult fluid algorithms tailoring them specifically to pediatric patients. After multiple focus groups with MSCH pediatric surgery and PICU leadership, we identified the physiologic parameters that we feel most accurately reflect intravascular volume – systolic blood pressure (SBP), heart rate (HR), base excess (BE), serum lactate levels, urine output (UO) and weight. These were incorporated into the proposed algorithms to guide fluid resuscitation. Inclusion and exclusion criteria are below listed in section F, Study Procedures. We hypothesize that the restricted fluid algorithm will yield the best results and lead to an improvement in clinical outcomes. This algorithm will allow practitioners in a wide breadth of clinical settings to follow clear and concise guidelines for fluid management in critically ill pediatric trauma patients.

**Overall Strategy, Methodology and Analyses:**

Currently, no standard exists to guide the management of crystalloid fluid administration in pediatric post-operative and trauma patients who share similar physiology. Both liberal and restricted fluid management strategies are in use, dependent on physician discretion. Therefore, we propose the first randomized controlled trial (RCT) comparing a liberal fluid management strategy to a restricted fluid management strategy in critically ill pediatric post-operative and trauma patients. This will be a comparative effectiveness study. Our objective is to conduct a multicenter (approximately 10 sites) RCT to determine whether liberal or restricted fluid administration leads to better outcomes in critically ill pediatric trauma patients.

The study PI and all site PIs will not be the prescribing physicians. PICU staff - not part of the study - will be treating patients enrolled in the study.

*Multi-Site Staff Training:* Dr. Duron (PI), in conjunction with IRB approved study personnel will provide training to PICU staff and trauma coordinators from participating institutions to ensure understanding and adherence to study algorithms. Conference calls and focus groups will be completed prior to site addition, bi-monthly, and as needed.

*Statistical Analyses:* Biostatisticians from the Center for Innovation and Outcomes Research (CIOR) at Columbia University Medical Center will provide statistical analyses to fulfill specific aims. REDCap (Research Electronic Data Capture) will be used for data management. REDCap is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages that will be used by the statistician; and 4) procedures for importing data from external sources. REDCap will provide stratified randomization to assign patients to either the liberal fluid arm or the restricted fluid arm, where we will stratify by site. After obtaining informed consent, research coordinators will create a new patient record in the REDCap database, enter patient data, and engage the REDCap randomization module. This easy to use interface will provide an immediate treatment group assignment, which will be stratified according to site. The data will be analyzed using intent-to-treat analyses. We will compare two different fluid resuscitation strategies, liberal fluid management vs. restricted fluid management.

The following statistical analyses will be employed to fulfill our first two specific aims:

*First Specific Aim (Primary Outcome Study):* The primary outcome is overall complications up to discharge. This is a binary indicator for whether subject has had any complication after being admitted to the PICU. These complications include: major complications – pulmonary edema, hemorrhage, hardware/deep cavity infection, anastomotic dehiscence, thrombosis, Acute Respiratory Distress Syndrome, abdominal compartment syndrome, or death; and minor complications – superficial wound infection, ileus, and pneumonia. We will estimate and compare the proportion of complications between the two groups using Pearson's chi-squared test. In order to obtain a composite evaluation of organ dysfunction, we will also compare Pediatric Logistic Organ Dysfunction (PELOD) scores for patients in each arm. The PELOD score has been validated as a useful measure of severity of multiple organ dysfunction in children (19). PELOD scores between groups will be compared using 2 sample t tests.

*Second Specific Aim (Secondary Outcome Study):* Secondary outcomes include - number of days on supplemental oxygen, number of days on ventilator, ICU length of stay, overall hospital length of stay, and each of the individual complications. For binary secondary outcomes, we will compare proportions and perform Pearson's chi-squared tests. For quantitative outcomes, we will examine the distribution of the variables and perform analyses as appropriate. For example, for quantitative variables that seem normal or close to normal, we may use 2 sample t tests. On the other hand, for quantitative variables that seem very non-normal, we may use nonparametric methods. We will describe and evaluate the comparability of our groups on key demographic variables and relevant baseline clinical variables and will adjust for them if necessary (e.g., gender, age). If there seems to be possible differences, we will use regression methods to compare the two treatment groups, while adjusting for other factors.

*Third Specific Aim:* In order to demonstrate that the proposed evidence-based "Restricted Fluid Algorithm" is feasible to implement and adhere to by healthcare practitioners caring for critically ill pediatric surgery and trauma patients, we have perform additional feasibility studies and focus groups to determine if algorithms are being adhered to in different hospital settings and what barriers exist that prevent compliance with algorithm. Some optimization has already occurred in the pilot study. This will allow the algorithm to be distributed and used widely in multiple different levels of care of pediatric surgery and trauma patients.

*Preliminary Power Analysis:* A 6-month analysis of the complication rate in our pediatric ICU identified an overall complication rate of 30%, which correlates with complication rates nationwide for pediatric ICUs. A power analysis to detect a 15% reduction in overall complication rate with 80% power, 2-sided analysis ($p = 0.05$) - requires 240 patients (120 in each arm). With a 40% participation rate and a 20% dropout rate, we anticipate that we will need 750 patients to be initially approached about the study to reach statistical significance for the primary outcome studied. If 10 tertiary and quaternary level pediatric centers participate in the study, and admit on average 30 critically ill surgical and trauma patients to their PICU per year, we will need approximately 2-3 years to complete the study.

**Potential Problems, Alternative Strategies, and Benchmarks:** We currently have confirmed commitment from 5 additional children's hospitals. We have engaged multiple other children's hospitals that have showed vested interest in the study and are currently reviewing the study proposal and algorithms to determine whether or not they will participate. We are confident that we will obtain participation from at least 10 tertiary and quaternary children's hospitals.

**Strategy to Establish Feasibility and Manage High Risk Aspects of Proposed Work:**

*Pilot Study:* Prior to launching the multicenter trial in all 10 centers, we have performed an initial pilot study in 2 New York City children's hospitals: Morgan Stanley Children's Hospital/Columbia University Medical Center and Northwell Health Cohen Children's Medical Center. This pilot study has examined implementation of the fluid management strategies, the feasibility of running an RCT, and estimates of treatment differences. What we have learned from the pilot study will inform our larger study. We have studied 30 patients in our pilot study. We have observed a difference in volume of fluid administered between the two groups although it is not statistically significant; we do not expect a statistically significant difference, as significance would likely require far more than 30 patients or extreme differences in fluid administration, and we want to compare fluid strategies within the current standard of care. We have optimized the protocol to 70% maintenance and half the bolus volume at 10cc/kg/hr for the restricted group. We have modified

the original algorithm to improve clarity and maximize adherence. Our outcome measures appear to be appropriately chosen and clinically relevant. The treatment algorithm is ready to be initiated in the multicenter trial in all 10 centers.

*Data Coordinating Center (DCC):* The Center for Innovation and Outcomes Research (CIOR) at the Columbia University Medical Center will function as the data coordinating center for the study. It will ensure the highest quality data collection and consistency between sites. The DCC will provide monthly enrollment reports to all sites. Sites will inform the DCC of user changes and the DCC will make associated updates to the database. This will help ensure only approved study personnel have access to the database. Additionally, the study database will have quality checks performed every 30 days. Study coordinating center personnel will review study data and send queries to sites when identifying discrepancies. Resolution of any discrepancies will be expected within 30 days.

*Transmission of data to the data-coordinating center:* Study participants are assigned a unique study number assigned by REDCap. The only study information retained at CUMC will be kept in a secure REDCap database. The other participating sites will only have access to their site's study information and participants' PHI on the REDCap database. The coordinating site (CUMC) will have access to each site's information on the REDCap database.

Each subject will be assigned a unique study identifier. The key to this study identifier will be kept on an encrypted hard drive at each participating site. Only the PI at each site will have access to this hard drive. Once the data has been de-identified, it will be sent via the internet by encrypted email directly to the lead institution PI who will review the data. Once reviewed, the datasheet will be sent by encrypted email to the DCC. The only study information retained at CUMC will be kept in the secure CIOR database. The other participating sites will only have access to their site's study information and participants' PHI on the CIOR database. The coordinating site (CIOR) will have access to each site's information on the CIOR secured database.

*Data Analysis:* The data-coordinating center (DCC) will provide the CIOR statistician at the lead institution with the data for data analysis. Once the analysis is complete, the DCC will inform the IRB of when it is appropriate for individual study sites to close out IRB oversight at that location.

*Data Safety and Monitoring Committee (DSMC):* In keeping with NIH requirements for multi-site clinical trials we have established a formal Data Safety Monitoring Committee (DSMC). The committee will meet every 25-30 recruited patients throughout the study period and review data provided by the Data Coordinating Center (DCC). The DCC is run by the Center for Innovation and Outcomes Research (CIOR) at CUMC. Adverse events will be prospectively monitored by the DCC and are expected to occur at a rate of 20-30%. This information will be given to the DSMC in order to allow an assessment of the safety of our trial. Adverse events include death and complications including pulmonary edema, hemorrhage, hardware/deep cavity infection, anastomotic dehiscence, thrombosis, Acute Respiratory Distress Syndrome, abdominal compartment syndrome, superficial wound infection, ileus, and pneumonia. These complications are the primary outcomes studied in this trial.

Adverse events that are serious, unexpected or unanticipated, and possibly related to the study treatments will be reported within 48 hours to the individual site Institutional Review Board (IRB) and the Data Coordinating Center (CIOR-CUMC). The DCC will then report these to the DSMC. The DSMC will review and approve the final trial protocol before enrollment begins. The DSMC is entirely independent of any trial investigator and any site that is actively enrolling patients into the study. The Chairman of the DSMC will be determined prior to the initiation of the trial.

*Ethics Board Approval:* The study is currently approved by CUMC IRB Committee - AAAR2083. Columbia University will be the lead institution for this multicenter prospective randomized trial.
For each participating institution, the local IRB will be responsible for the review and approval of research conducted for that respective study site. The PI at the lead institution will maintain records of IRB/ethics committee review and approval of all protocols and consent forms for all collaborating sites throughout the duration of the study. The PI at the lead institution will be responsible for ensuring that all modifications and renewals are reviewed and approved

appropriately; i.e., modifications are approved prior to their implementation and protocols and consent forms are renewed in a timely manner with no lapse in the renewal.

*Interim Analyses:* We plan for two interim analyses for efficacy at 1/3 and 2/3 enrollment. The boundaries for early stopping will be calculated, using the Lan-DeMets alpha spending function with O'Brien-Fleming type boundaries.

**E) RECRUITMENT AND CONSENT**

*Recruitment:* The first contact with a potential subject will be from their treating physician when possible. Once the potential subject has given verbal agreement, this will be documented by the physician in the medical record and the study personnel will be allowed to contact the potential subject. Either the research coordinator or the PI will then approach the patient to discuss the study. Only the research coordinator, PI, or medical personnel approved by the IRB will obtain consent to participate in the study. This will be replicated at all sites involved in the study.

Specifically, patients (through interaction with the parents/guardians) will be recruited when the patient presents after trauma, then the parent will be approached within 12 hours after arrival in the PICU at a time that is found to be appropriate by the treating physician. Only patients with an expected PICU stay of over 24 hours will be approached to participate in the study. Recruitment will be performed by study personnel once the treating physician has obtained permission from the subject's parent.

We plan on recruiting English and Spanish speakers for the study. The consents are written and explained in English and Spanish. We have ensured full understanding of the Spanish consent by use of verified Spanish interpreters for consenting. Spanish speaking healthcare providers will be available throughout the study to answer any questions to Spanish speaking subjects. A fluent Spanish speaker and will be available 24 hours a day.

*Consent:* As described above, subjects' parents/guardians will be approached after trauma, then the consent will be obtained from parent after arrival in the PICU at a time that is found to be appropriate by study personnel.

Every effort will be made to obtain signed informed consent by the parents/guardians as soon as possible. However, the nature of the hospital stay for some eligible patients, particularly for trauma patients that may have been transferred from another facility is such that parents may not be readily available in the PICU. When the treating physician determines the patient may be a good candidate for the trial but parent/guardian is unavailable for written consent, phone consent will be obtained. The research coordinator or PI will provide the parent with the study information and answer any questions the parents have. If parental consent is given over the phone, the patient will be randomized to treatment group so that providers can determine the treatment plan for the participant. The consent process will continue when the parent is again at the hospital where written consent will be obtained. After obtaining informed consent, research coordinators will create a new patient record in the REDCap database, engage the REDCap randomization module, and enter patient data. This easy to use interface will provide an immediate treatment group assignment, which will be stratified according to site. Randomization and initiation of treatment per study guidelines has to begin within 12 hours of arrival to the PICU in order to be included in study.

Again, we plan on recruiting English and Spanish speakers for the study. The consents will be written and explained in English and Spanish. We will ensure full understanding of the Spanish consent by use of verified Spanish interpreters for consenting when consent is done over the phone and in writing. Spanish speaking healthcare providers will be available throughout the study to answer any questions to Spanish speaking subjects. The PI is a fluent Spanish speaker and will be available 24 hours a day. It has been confirmed that a Spanish interpreter is available 24 hours a day at all confirmed sites.

Consenting of illiterate parents will be completed by detailed explanation of the study and treatment involved in lay terms. Social workers will be available to assist if there is difficulty in comprehension.

Assent will be obtained for patients ≥ 8 years old who are capable of assent at the time of consent; this excludes developmentally disabled and unconscious patients.

**F) STUDY PROCEDURES**

- All study procedures have been discussed and agreed upon by participating PICU and pediatric surgery staff during prior focus groups. Study procedures will continue to be analyzed for safety and effectiveness during the study.
- As described above, eligible patients will be consented and randomized to a treatment arm within 12 hours of arrival to the PICU. Patients expected to be discharged from the PICU within 24 hours will not be included in the study.
- Patients are admitted to the PICU either post-operatively or from the ED. Their initial vitals will be within limits not requiring vasopressor support. Vitals will be checked per PICU protocol (4 times per hour)
- The Treatment Algorithm, Inclusion/Exclusion/Algorithm Specifications, and Study Protocol will be stored in a secured folder in the PICU for easy access by participating PICU staff during intervention/treatment.

**Inclusion/Exclusion Criteria:**

*Inclusion Criteria:*

- Trauma patients older than 6mo and younger than 15yo admitted to the PICU
- Patients admitted to the PICU directly from the ED
- Patients admitted to the PICU from the OR
- Patients transferred to PICU from outside facility ER (need to have been in ER 12hours or less)

*Exclusion Criteria:*

- Patients transferred to PICU from outside PICU or inpatient floor
- Patients transferred to PICU from outside facility ER if >12hours
- Patients expected to be discharged from the PICU within 24 hours
- Patient with congenital heart disease as defined by a congenital cardiac defect requiring surgery or medication
- Patient with diagnosis of chronic cardiac condition (e.g. hypertension, cardiac arrhythmia)
- Patients with chronic kidney disease as defined by an abnormality of kidney structure or function, present for more than 3 months, with implications to health
- Post-operative transplant, cardiac, and neurosurgical patients
- Patients with traumatic brain injury
- Patients with any disease that may affect baseline blood pressure and heart rate (endocrine disorders, certain genetic disorders, mitochondrial diseases)
- Hypotension requiring vasopressor therapy
- If massive transfusion protocol initiated

**Intervention:**

Please see separate treatment algorithm diagrams for additional schematic of intervention explained below.

*Initial RESUSITATIVE PHASE:*

- All patients in the study are initiated on maintenance isotonic balanced crystalloid IV fluid (LR or PlasmaLyte) during the initial (resuscitative) phase of their treatment. The calculation of maintenance rate will be based on the standard 4-2-1 formula for maintenance fluid rate for patients < 110kg:
    - 0-10kg – 4mL/kg
    - 11-20kg – 2mL/kg
    - >20kg – 1mL/kg
    - For example: a 34kg child will be administered 10x4+10x2+14x1=74cc/kg/hr of isotonic IV fluids during the first 24 hours after trauma or operation
- In the **LIBERAL Non-bleeding and LIBERAL Bleeding** groups maintenance will be standard **4-2-1** as described above
    - For patients > 110kg, maintenance will be a standard **150mL/hr**
- In the **RESTRICTED Non-bleeding and RESTRICTED Bleeding** groups maintenance will be **70% of 4-2-1** calculation.
    - For example: For example: a 34kg child will be administered 0.7*(10x4+10x2+14x1)=52cc/kg/hr of isotonic IV fluids during the first 24 hours after trauma or operation
    - For patients > 110kg, maintenance will be a standard **105mL/hr** (70% of 150mL/hr)

- Change IN ANY ONE OF the following vital signs or blood results will prompt additional intervention:
    - Decrease in Systolic Blood Pressure (SBP) by >20% from 50$^{th}$ percentile for that age, weight, and gender according to NIH reference chart – confirmed on recheck
    - Increase in Heart Rate (HR) by >20% from 50$^{th}$ percentile for that age and weight according to NIH reference chart – confirmed on recheck
    - Base excess (BE) < -5mmol/L
    - Blood Lactate > 2mmol/L

IN ADDITION TO:

- Urine Output (UO) < 1mL/kg/hr in patients < 50 kg, or <50mL/hr in patients > 50 kg

- **For Urine Output:**
    - If Foley in place will check UO every 1 hour
    - If Foley not in place will check UO every 4 hours
    - If UO not checked after 4 hours, will document reason why (e.g. urinary retention, older patient sleeping, etc.)
- In **LIBERAL Non-bleeding group**, patients will be bolused **20mL/kg** isotonic balanced crystalloid fluid (LR or PlasmaLyte) for patients under 50kg
    - For patients ≥ 50kg, patients will be bloused a standard **1L**
- In **RESTRICTED Non-Bleeding group**, patients will be bolused **10mL/kg** isotonic balanced crystalloid fluid (LR or PlasmaLyte) for patients under 50kg
    - For patients ≥ 50kg, patients will be bloused a standard **500mL**
- If patients are categorized as "Bleeding" by the operating surgeon or treating pediatric trauma surgeon, then they will be randomized into a "Bleeding" arm of the protocol and receive treatment per those guidelines. A "Bleeding" patient can be a patient that is deemed to have ongoing bleeding coming out of surgery. A "Bleeding" patient can be a patient that presents with hemorrhage from trauma. The operating surgeon or trauma surgeon will make that determination and communicate it to the PICU treating physician.
- **In both LIBERAL Bleeding group and RESTRICTED Bleeding group, patients will be transfused if they meet agreed upon transfusion triggers (national standards)**:
    - If Hb <7, then transfuse 10mL/kg Packed Red Blood Cells (PRBC)
    - If Platelets <50, then transfuse 10ml/kg platelets
    - If INR>1.5, then transfuse 10mL/kg Fresh Frozen Plasma (FFP)
- Patients will be transfused with PRBC, platelets, or FFP by weight up to 250mL. Patients above 25kg will get a standard 250mL of product per transfusion (1 unit).
- The difference in treatment in the Bleeding groups occurs when the patient does not meet strict criteria for blood product transfusion but shows signs of hypovolemia, as evidenced by decrease in SBP, increase in HR, increase in base excess, increase in lactate or decrease in urine output. For these patients, treatment will be as follows:
- **In LIBERAL Bleeding group not meeting strict transfusion criteria but showing signs of hypovolemia**, patients will be either transfused blood products 10mL/kg or bolused 20mL/kg isotonic balanced fluid (LR or PlasmaLyte) per physician discretion
- **In RESTRICTED Bleeding group not meeting strict transfusion criteria but showing signs of hypovolemia**, patients will be either transfused blood products 10 mL/kg or bolused 10mL/kg isotonic balanced fluid (LR or PlasmaLyte) per physician discretion

*DIURESIS PHASE:*

- If PICU treating physician determines that patient has been adequately resuscitated – which is determined by clinical criteria set forth by treating physician then the patient may switch to "Diuresis Phase" of protocol – this can be initiated ONLY AFTER 24hours have elapsed since trauma or surgery
- If at 24 hours, patient is not yet in diuresis phase then continue to manage per initial fluid management strategy
- Treatment during diuresis phase revolves mainly around Urine Output (UO), which is measured and documented per PICU protocol
- **For LIBERAL group < 50kg in Diuresis Phase**:
    - If UO < 2mL/kg/hr then continue maintenance IV fluid rate and bolus as per initial phase (Liberal arm)

    - If UO > 2mL/kg/hr, and Lactate, SBP, HR, Cr normal then decrease IV fluid rate to ½ maintenance rate and then KVO when taking regular feeds
- **For LIBERAL group > 50kg in Diuresis Phase**:
    - If UO < 100mL/hr then continue maintenance IV fluid rate and bolus as per initial phase (Liberal arm)
    - If UO > 100mL/hr, and Lactate, SBP, HR, Cr normal then decrease IV fluid rate to ½ maintenance rate and then KVO when taking regular feeds
- **For RESTRICTED group < 50kg in Diuresis Phase:**
    - If UO < 1mL/kg/hr then continue IV fluids at maintenance rate and bolus as per initial phase (Restricted arm)
    - If UO 1-2mL/kg/hr then decrease IV rate to ½ maintenance rate
    - If UO >2mL/kg/hr, and Lactate, SBP, HR, Cr nl then KVO IVF +/- administer Furosemide for goal UO >2-4mL/kg/hr until euvolemic (back to baseline weight, or total daily fluid in = total fluid out)
- **For RESTRICTED group > 50kg in Diuresis Phase:**
    - If UO < 50mL/hr then continue IV fluids at maintenance rate and bolus as per initial phase (Restricted arm)
    - If UO is 50-100mL/kg/hr the decrease IV rate to ½ maintenance rate
    - If UO > 100mL/hr, and Lactate, SBP, HR, Cr are normal then KVO IVF +/- administer Furosemide for goal UO > 100-200mL/hr until euvolemic (back to baseline weight or total daily fluid in = total daily fluid out)
- Frequency of labwork is per physician discretion except that if intervention is performed in response to lab value, then repeat lab value is expected to be drawn within 1 hour of completion of intervention
- If patient becomes hemodynamically unstable and is not responsive to fluid/blood administration and a vasopressor needs to be started then patient comes off protocol - reason has to be recorded on the "Off Protocol Record Form"

Treating physician can have patient come off protocol at any given time – reason has to be recorded on "Off Protocol Record Form"

**Criteria For Discontinuation:**

- Patients will continue to follow study protocol until the following timepoints:
    - patient is transferred to the pediatric ward from the PICU
    - when euvolemia has been reached – this is defined as weight equal to admission weight (when weight is checked daily in PICU) or when total volume in is equal to total volume out.
    - after 1 week of treatment

Whichever of these parameters first occurs is the timepoint at which patient comes off protocol. Again, reason is recorded in "Off Protocol Record Form"

- As stated above, If patient becomes hemodynamically unstable and is not responsive to fluid/blood administration and a vasopressor needs to be started or if treating physician wants to come off protocol then patient comes off protocol – reason is recorded in "Off Protocol Record Form"
- As stated above treating physician can remove patient from protocol at any time per clinical judgement – reason has to be recorded on the "Off Protocol Record Form"

**Data Entry**: Patient's chart will be reviewed and data extracted on a daily basis by study personnel. It will be entered daily into REDCap. Questions or concerns will be brought up with treating physician team on a daily basis during a time that does not interfere with patient care.

## G) ANTICIPATED OUTCOMES, PREDICTED RESULTS, TARGETED EXTERNAL GRANT APPLICATIONS

We anticipate that patients in the Restricted Fluid arm will have improved outcomes. We predict that the primary outcomes will be improved in these patients. They will have fewer overall complications, including all listed above. They will also have a decreased need for respiratory support. They will have fewer days on supplemental oxygen or on the ventilator. Their hospital length of stay and their overall hospital length of stay will be shorter. We plan on applying for multiple external grants. We have been awarded the Childress Institute for Pediatric Trauma (CIPT) Scholarship and in the near future plan to apply for the Eastern Association for the Surgery of Trauma (EAST) Trauma Research Grant, the American Pediatric Surgical Association (APSA) Foundation Grant, and the National Institutes of Health (NIH) Exploratory/Developmental Research Grant Award (R21).

## H) PROJECT TIME LINE, SPECIFIC PROJECT DELIVERABLES

Educate nurses and physicians on protocols, data entry in 2 months. Enroll enough patients for 10-site RCT within 3 years, performing interim analyses at 1/3 and 2/3 study period. Final data analyses should be completed within 6 months after the trial is closed. Presentations at national conferences and publication of manuscript should occur within a year following closure of trial.

**I) LITERATURE CITED**


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