MEDICAL PROTOCOL (HRP-590)
PROTOCOL TITLE: Magnesium sulfate as adjuvant analgesia and its effect on opiate use by post-operative transplant patients in the pediatric ICU.
VERSION DATE: 06/09/2022
**INSTRUCTIONS:**

**ANCILLARY REVIEWS**

| **Which ancillary reviews do I need and when do I need them?** Refer to HRP-309 for more information about these ancillary reviews. | | | |
|---|---|---|---|
| **Select yes or no** | **Does your study…** | *If yes…* | ***Impact on IRB Review*** |
| ☐ **Yes** ☐ **No** | Include Gillette resources, staff or locations | *Gillette Scientific review and Gillette Research Administration approval is required. Contact: research@gillettechildrens.com* | **Required prior to IRB submission** |
| ☐ **Yes** ☐ **No** | Involve Epic, or Fairview patients, staff, locations, or resources? | *The Fairview ancillary review will be assigned to your study by IRB staff Contact:* ancillaryreview@Fairview.org | **Approval must be received prior to IRB committee/ designated review.** **Consider seeking approval prior to IRB submission.** |
| ☐ **Yes** ☐ **No** | Include evaluation of drugs, devices, biologics, tobacco, or dietary supplements or data subject to FDA inspection? | *The regulatory ancillary review will be assigned to your study by IRB staff Contact: medreg@umn.edu* *See: https://policy.umn.edu/research/indide* | |
| ☐ **Yes** ☐ **No** | Require Scientific Review? Not sure? See guidance on next page. | *Documentation of scientific merit must be provided. Contact: hrpp@umn.edu* | |
| ☐ **Yes** ☐ **No** | Relate to cancer patients, cancer treatments, cancer screening/prevention, or tobacco? | *Complete the CPRC application process. Contact: ccprc@umn.edu* | |

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| ☐ **Yes**<br>☒ **No** | Include the use of radiation? (x-ray imaging, radiopharmaceuticals, external beam or brachytherapy) | *Complete the AURPC Human Use Application and follow instructions on the form for submission to the AURPC committee.*<br>*Contact: barmstro@umn.edu* | **Approval from these committees must be received prior to IRB approval;**<br><br>**These groups each have their own application process.** |
| ☐ **Yes**<br>☒ **No** | Use the Center for Magnetic Resonance Research (CMRR) as a study location? | *Complete the CMRR pre-IRB ancillary review*<br>*Contact: ande2445@umn.edu* | |
| ☐ **Yes**<br>☒ **No** | Include the use of recombinant or synthetic nucleic acids, toxins, or infectious agents? | *Complete the IBC application via eprotocol.umn.edu*<br>*Contact:* | |
| ☐ **Yes**<br>☒ **No** | Include the use of human fetal tissue, human embryos, or embryonic stem cells? | *Contact OBAO for submission instructions and guidance* | |
| ☒ **Yes**<br>☐ **No** | Include PHI or are you requesting a HIPAA waiver? | *If yes, HIPCO will conduct a review of this protocol.*<br>*Contact: privacy@umn.edu* | |
| ☐ **Yes**<br>☒ **No** | Use data from the Information Exchange (IE)? | *The Information Exchange ancillary review will be assigned to your study by IRB staff*<br>*Contact: ics@umn.edu* | **Approval must be received prior to IRB approval.**<br><br>**These groups do not have a separate application process but additional** |
| ☐ **Yes**<br>☒ **No** | Use the Biorepository and Laboratory Services to collect tissue for research? | *The BLS ancillary review will be assigned to your study by IRB staff.*<br>*Contact: cdrifka@umn.edu* | |
| ☐ **Yes**<br>☒ **No** | Have a PI or study team member with a conflict of interest? | *The CoI ancillary review will be assigned to your study by IRB staff*<br>*Contact: becca002@umn.edu* | |

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| ☒ **Yes**<br>☐ **No** | Need to be registered on clinicaltrials.gov? | *If you select "No" in ETHOS, the clinicaltrials.gov ancillary review will be assigned to your study by IRB staff Contact: kmmccorm@umn.edu* | **information from the study team may be required.** |
| ☒ **Yes**<br>☐ **No** | Require registration in OnCore? | *If you select "No" or "I Don't Know" in ETHOS, the OnCore ancillary review will be assigned to your study by IRB staff Contact: oncore@umn.edu* | **Does not affect IRB approval.** |

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| **Protocol Title** | Magnesium sulfate as adjuvant analgesia and its effect on opiate use of post-operative transplant patients in the pediatric ICU. |
| **Principal Investigator/Faculty Advisor** | Name: Dr. Gwenyth Fischer |
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| **Scientific Assessment** | HRPP facilitated scientific assessment. |
| **IND/IDE # (if applicable)** | 144569 |
| **IND/IDE Holder** | Gwenyth Fischer |
| **Investigational Drug Services # (if applicable)** | 5570 |
| **Version Number/Date:** | Version1.06-06/09/2022 |

**PROTOCOL COVER PAGE**

**REVISION HISTORY**

| Revision # | Version Date | Summary of Changes | Consent Change? |
|---|---|---|---|
| 1 | 2/15/2020 | Clarify blood draw spacing if infusion turned off, clarify COVID influence on patient enrollment and consent procedure, minor adjustments to data build | No |
| 2 | 12/15/2021 | Updated co-investigaor status and IDS#, updated timing of MgSO4 initiation in liver transplants (4.1), eliminated need for dose conversion calculations – pump library was fixed (13.1), deleted method for MME calculation with identification of relevant literature (15.1) | No |
| 3 | 04/12/2021 | Updated version date, minor formatting corrections (8.1,8.2), added new exclusion criteria (8.2), added new withdrawal criteria clarifier (12.1), increased language regarding potential for less patient enrollment (10.1), added risk of protocol deviation (13.1), added additional monitoring element to prevent protocol deviation (18.1) | No |
| 4 | 6/9/2021 | Provided additional wording responding to stipulation letter for continued magnesium approval (18.1) | No |
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**Table of Contents**

**ABBREVIATIONS/DEFINITIONS**

Include any abbreviations or definitions for key or technical terms you use in your protocol.

- PICU: pediatric intensive care unit
- TPIAT: total pancreatectomy and islet cell autotransplantation
- CTSI: Clinical and Translational Science Institute
- BPIC: Best Practices Integrated Informatics Core
- IDS: investigational drug service
- IND: investigational drug
- FDA: Food and Drug Administration
- UMN: University of Minnesota
- PI: principal investigator
- EMR: electronic medical record
- MgSO4: magnesium sulfate
- PCA: patient-controlled analgesia (machines where patient can press button to have medicine delivered, giving them more personalized control of their care)
- POD#0: post-operative day #
- OR: operating room
- T&A: tonsillectomy and adenoidectomy
- IV: intravenous
- pt: patient
- PO: per os (latin for 'by mouth')
- PRN: pro re nata (latin for 'as needed')
- mg: milligram
- kg: kilogram
- hr: hour
- AE: adverse event
- SAE: serious adverse event
- CRF: case report form
- PACCT: Pediatric Pain and Advanced/Complex Care Team
- CRNA: certified registered nurse anesthetist

## 1. Objectives

*1.1.* Purpose: To use magnesium sulfate as adjuvant analgesia by implementing a treatment protocol in order to determine whether can benefit pediatric pain in post-operative transplanted patients and decrease overall opioid consumption.

## 2. Background

*2.1.* Significance of Research Question/Purpose: Our study's purpose would be to improve analgesia in TPIAT (total pancreatectomy and islet cell autotransplant) and liver transplant recipients in the PICU, and to expand growing literature regarding magnesium as an analgesic, including in a yet-studied population. There is currently some promising data that MgSO4 can be beneficial as an analgesic in certain operative and post-operative pediatric patients, though data remains mixed depending on the method of magnesium delivery, as well as the dosing used and study design. Pain remains a significant source for morbidity in post-transplant pediatric patients, and to our knowledge use of magnesium for analgesia has not been studied in these populations. Opioid-sparing medication and targeting new analgesic options is an important and growing research topic in medicine.

*2.2.* Preliminary Data: To our knowledge there is no data regarding magnesium use for pain control in post-operative transplant patients, despite growing literature of effective use of magnesium as an analgesic (both adults and pediatrics). There is data in MgSO4 pediatric analgesia studies, extrapolated data from continuous MgSO4 infusions in asthmatics, and numerous adult studies, the combination of which support safety for our intended infusion dosing in our study.

*2.3.* Existing Literature: Early data regarding MgSO4 use as adjuvant analgesia dates back to the late 90's in adult literature (2), and has since been studied in a wide variety of those populations, with some meta-analysis data now showing efficacy as well (3-13). Pediatric literature often lags behind, however now also has growing data over the past two decades. Much of the pediatric analgesic-specific data is in tonsillectomy populations, which has mixed but promising results on efficacy depending on the method of delivery as well as outcome measure studied (14,15,22-25,28-29). Potentially more comparable pediatric populations to our proposed study population include osteotomies in cerebral palsy and scoliosis repairs, which both tend to have more analgesic requirement than T&A. Both of these populations have been studied and shown to have decreased opioid needs and/or pain scores with magnesium analgesia (17,18). Most statistically significant beneficial data of MgSO4 use cites a bolus IV dose in the OR, followed by a continuous infusion during the procedure. Adult studies have shown potential benefit in extending this infusion beyond the OR as well (40,41). Given the increased and prolonged opioid needs in the PICU course of both liver

transplant and particularly TPIAT patients, we intend to implement a combination of intra-operative and post-operative magnesium protocol. To our knowledge there is no definitive therapeutic window for magnesium's analgesic effect, and studies vary as to what supra-physiologic levels are obtained based on their derived infusion protocol. Comparable intra-operative infusion doses in pediatric analgesic studies range from as low as 30 mg/kg + 10 mg/kg/hr (25) and 50 mg/kg + 8 mg/kg/hr (17) to as high as 50 mg/kg + 15 mg/kg/hr (18). The study at our proposed dosing had levels of 3.2 mg/dL immediately post-op (18). Infusions of higher doses have been used safely in pediatric asthma studies, including doses of 50-75 mg/kg + 40 mg/kg/hr for 4 hours, reaching interquartile levels of high 3's to mid 4's mg/dL (37). In adult studies prolonged infusions have been used for subarachnoid hemorrhage targeting higher ranges of 4-6 mg/dL for up to 10 days duration (38,39). Adult studies have also demonstrated efficacy in infusion protocols beyond the operative period (40,41). One protocol of 30 mg/kg + 10 mg/kg/hr was used for 48 hours in thoracotomy patients with levels of 2.8 +/- 0.3 mg/dL at conclusion (41). Prolonged infusions in pediatrics beyond 24 hrs in the literature to our knowledge exist only in asthma studies, including one with average duration of ~4 days (42). None of the above studies encountered any clinically significant magnesium side effects, and only transient diplopia and muscle weakness was reported in the adult subarachnoid hemorrhagic study when levels reached 6 mg/dL (symptoms resolved with lowering dose). According to DynaMED and Micromedex searches on magnesium, normal levels may range 1.5 - 2.5 mEq/L (equivalent to 1.8-3.1 mg/dL), and toxic hypermagnesemic levels are typically not seen until >4 mEq/L (4.86 mg/dL), which does not yet include many of the hemodynamic and EKG changes (typically at >5 mEq/L or 6.08 mg/dL). Most background data in our referenced sources cite ~4.5-5 mg/dL as potential sources of clinically relevant magnesium toxicity. We intend to target levels well below this and will avoid adverse effects by checking serial magnesium levels and titrating our infusion dose down if needed. Level checks and titration plan is determined from existing pharmacokinetic/pharmacodynamic data, discussions with our pharmacy team, which is standardly involved with safety modifications of all admitted PICU patients, and recommendations from the FDA during the IND process. The significance and rationale for this study has been alluded to above, namely due to the extensive pain that post-operative transplant children endure, and our clinical duty to treat this medical problem (benevolence). Our post-operative patients are scheduled on a number of analgesic modalities simultaneously, including acetaminophen, NSAIDs, opioids, ketamine, non-pharmacologic intervention (child life, music therapy, etc), and even procedural (paravertebral block in TPIAT patients) - stressing both the difficulty of their pain control as well as the need for safe alternatives. Additionally, the growing threat of the opioid crisis and shortage has emphasized the need for adjuvant analgesic options in a multitude

of patient populations to better distribute what opioids are available (justice). Magnesium is one of the potential adjuvants that we hope to expand existing literature on by investigating a yet-studied population. Secondary benefit from the use of MgSO4 is the optimization of hypomagnesemia, which is especially common in ICU populations, including post-transplant patients who are often on tacrolimus for immunosuppression (43-45). Hypomagnesemia in itself is associated with hypokalemia, hypocalcemia, hypoalbuminemia, metabolic alkalosis, and prolonged PICU stays (45). Based on its safety profile outlined above, promising literature search, and optimal patient population (high analgesic requirement), we feel that this study has tremendous potential for scientific significance in pediatric patients.

## 3. Study Endpoints/Events/Outcomes

*3.1.* Primary Endpoint/Event/Outcome: Primary outcome focuses on the total opioid requirement (morphine equivalent per body weight) over the operative and post-operative PICU course (which may range upwards of 7 days in some transplant cohorts). The hypothesis is that magnesium sulfate use will decrease this dosage compared to controls, however measurements will be used to determine whether the intervention does not have any statistical difference as well (or even increases doses, which would be otherwise unexpected in the literature). We intend to pilot 30 prospective transplant patients (liver, TPIAT). Retrospective control data will consist of the last 60 transplants (30 liver, 30 TPIAT), which was determined based on original power analysis targets for a larger-based study anticipated in the future. The study will be stopped prematurely if during obligated data reviews it is determined that opioid needs are increasing. The study will also be halted if 2 patients develop clinically significant adverse reactions secondary to magnesium, at minimum until able to further review dosing and protocols. If arrhythmia (other than transient bradycardia), respiratory failure, or coma are encountered once (also deemed secondary to magnesium), the study will be halted immediately with that patient. Per above, if encountering more frequent anemia than typical post-transplant, the study will be halted to evaluate lab frequency's effect. The study will also be halted for further review if there is a dosing error. A list of data measures is provided in a secondary attachment with this protocol.

*3.2.* Secondary Endpoint(s)/Event(s)/Outcome(s): Secondary outcome data will evaluate total opioid use by post-operative day (i.e. POD#1, POD#2, POD#3, etc) to help determine any variance in effect based on proximity to the surgery as well. Secondary outcomes will also focus on other opioid variables, including amount of 'requested' (PRN) opioids versus what is scheduled. Secondary outcomes will also include opioid side effect data, since these would hypothetically be less if MgSO4 does indeed lessen opioid needs. We will collect 'pain scores' as well, however literature suggests these are often difficult to

interpret and do not always correlate well with true comfort measures. Other data collection listed below will be used to help track safety data regarding magnesium effects, correlations between magnesium level and opioid variables, other analgesic dosing, as well as general statistical comparisons such as sex, type of surgery, and age. A list of data measures is provided in a secondary attachment with this protocol.

## 4. Study Intervention(s)/Investigational Agent(s)

*4.1.* Description: MgSO4 is a pharmacological agent which will be administered intravenously as a 30-minute bolus dose of 50 mg/kg (maximum 2 grams) in the OR, followed by a 15 mg/kg/hr IV infusion for an additional 48 hours or once the patient has transferred out of the PICU, whichever comes first. The bolus will be given after anesthesia induction for TPIAT patients, and after reperfusion of the transplanted liver for liver transplant patients (this is deemed by surgeon to pose less hemodynamic risk). Of note, it is not anticipated that our patient population would leave the PICU prior to 48 hours. Standard bolus dosing of MgSO4 in pediatrics is 25-75 mg/kg, so per the above literature search 50 mg/kg seems a confirmed safe dosing. Similar dosing protocols using a bolus and infusion which have been studied for analgesia in children without side effect in the literature include the following: 50 mg/kg then 15 mg/kg/hr (18,20), 30 mg/kg then 10 mg/kg/hr (14,25), 50 mg/kg then 8 mg/kg/hr (17). Our proposed 50 mg/kg + 15 mg/kg/hr infusion dose has been utilized effectively and safely at the adult level as well (5,49). Dosing as high as 100 mg/kg then 40 mg/kg/hr has been used in tetanus. To our knowledge, MgSO4 for analgesia remains 'off-label' use, unless discussing for headache pain (used commonly in emergency room medication 'cocktails' for migraines). It is known however that magnesium acts antagonistically on the NMDA receptor, a common nociceptor, one also targeted by ketamine (1). MgSO4 will be delivered at concentration of 100 mg/mL via patient's central line (placed in all transplants regardless of study intervention). MgSO4 is also a physiologically vital electrolyte in the human body, and one that is replaced frequently in the ICU, including in the post-operative transplant population. To avoid nearing toxic magnesium levels, we will titrate medication dosing to be below 3.5 mg/dL. Total magnesium level will be checked in the OR following bolus dose, every 2 hours throughout the transplant procedure, at the initial PICU transfer and every 4 hours [expected window +/- 1 hour] for the remainder of infusion. Other electrolytes (including potassium, ionized calcium, phosphorus) will be checked at least daily (sometimes more if deemed appropriate for other standard of care transplant requirements, which is typically every 6 hours). If any magnesium level is above target, infusion dose will be decreased by 5 mg/kg/hr. These adjustments are based on pharmacokinetic-pharmacodynamic data and pharmacist expertise at the UMN. If magnesium infusion is at any time decreased to 0 mg/kg/hr based on these levels, it will not

be restarted. Should the infusion be discontinued, once magnesium levels normalize we will plan to check magnesium levels at discretion of primary team rather than study intervals, so as to minimize risk of anemia and excessive accessing of central line. If levels are not able to be drawn due to some other unpredicted variable (patient participating in physical therapy, patient escorted down to gift shop, patient had emergent surgical intervention for other reasons, etc), blood draw will be performed at earliest availability. This is standard of care for any serial blood draw ordered on the unit. If there is an adverse event that there is concern magnesium may be contributing, the infusion will be immediately turned off until further investigation deems safe to restart. Any adverse event deemed secondary to magnesium will result in indefinite discontinuation of the infusion, notification of safety monitor, and review of study protocol as outlined elsewhere. This is discussed further in risk sections. Despite magnesium being an approved elemental agent, based on the above protocol and the extended duration of magnesium infusion compared to available literature, as well as the absence of previous research in our targeted population, this proposed project was submitted to and approved by the FDA under an IND application. Based on the sources discussed above in existing literature section, our dosing protocol has been tried intraoperatively in both pediatrics and adults without side effect and demonstrated levels below which cause hemodynamically relevant side effects. Further data (asthma in pediatrics, multiple purposes in adults) have demonstrated prolonged durations of magnesium infusion at comparable doses without adverse effects, including durations longer than our proposed 48 hours. Additionally, some studies mentioned reached higher levels than our proposed target and remained free of side effect.

*4.2.* Drug/Device Handling: This is an IND research study, in which case the Investigational Drug Service at UMN will monitor handling of magnesium including ordering, storage, and handling of the medication. OnCore programming will be used for IDS-monitoring and study's protocol schedule. Costs for medication and drug levels will be paid for by grant funding. Nurses perform 2-person checks to confirm all ICU-delivered medications, which will include MgSO4. This includes checking name of medication, dose, and infusion rate when starting the medication. There will be no change-over to a new MgSO4 bag at transfer from OR to PICU. The medication is already currently ordered and stored at the UMN, so would not otherwise require any new/additional hospital design, other than pharmacy and IDS tracking any shortage of supply.

*4.3.* Biosafety: n/a

*4.4.* Stem Cells: n/a

*4.5.* Fetal Tissue: n/a

## 5. Procedures Involved

*5.1.* Study Design:

Experimental Group: Prospective Cohort of next 30 incoming liver and TPIAT transplant children which meet inclusion criteria. Due to the more difficult predictability of when liver transplants occur, and to ensure adequate enrollment of 30 patients occurs within the 3-year pilot duration, we have chosen not to have a 50/50 balanced prospective cohort.

Control Group: Control will be via retrospective chart review of the last 60 transplant patients from the same population (liver, TPIAT) with same surgeon. Intervention and data collection will be as outlined elsewhere in protocol.

*5.2.* Study Procedures:

Experimental Group: There will be no operative procedures per study parameters (though the transplantation procedure itself as well as any secondary procedures from complications are otherwise per standard of care). Patient's medical record will be reviewed for basic eligibility criteria (history of myasthenia gravis or heart block). If female and of reproductive age, patient will have a urine B-hCG, which is routine prior to any abdominal surgery. The only prospective study procedure will be the magnesium protocol previously outlined, where IV MgSO4 will be delivered as a 30-minute bolus dose of 50 mg/kg (maximum 2 grams) in OR followed by a 15 mg/kg/hr infusion initiated immediately after (i.e. in OR as well) until conclusion of PICU stay or 48 hours, whichever comes first. Magnesium levels will be monitored throughout the duration of the infusion per above - every 2 hours in OR starting after bolus dose, then every 4 hours [expected window +/- 1 hour]. There are no other baseline visits or follow-up visits independent of the PICU stay and initial consent process. We do not anticipate this study intervention impacting workflow significantly, as infusion medications are standard interventions in the PICU, and these patients already have frequent blood draws. A study schedule with these interventions will be created via OnCore program to ensure compliance with protocol. Data outcomes will be collected from epic EMR at the conclusion of each patient's ICU admission by co-investigator and medical student researcher and stored in REDCap. All collected data is via EMR, so no surveys/scripts/forms are needed for data collection. Specifically, the EMR will be accessed for appropriate transplant patient, followed by selecting the appropriate surgical encounter (which would be current), followed by selecting only specific portals in Epic EMR where intended data elements are located (for example: Intake/Output section, or results review -> magnesium level, etc). Only specific data collection pathways will be targeted while in a patient's medical chart. There are no other drugs/devices involved in study or that would alter MgSO4 delivery. Similarly, there are no out-of-hospital prescriptions or interference during the ICU admission which would alter the study protocol. Any out-of-hospital contact (i.e. pre-admission consent if performed) will include adherence to COVID precautions per hospital guidelines.

Control Group: For collection of control data, a MRN list of the most recent 60 transplant patients under the same surgeon at this institution (30 liver, 30 TPIAT) who have not opted out of research will be obtained via UMN's Best Practices Integrated Informatics Core (BPIC), followed by access to EPIC EMR outside of the Information Exchange to review patient's chart and collect for intended outcomes, which are also uploaded into RedCap. This will be done in identical manner as that for prospective data collection — the EMR will be accessed for appropriate patient by MRN, followed by selecting the appropriate surgical encounter by date, followed by selecting only specific portals in epic where intended data elements are located (for example: Intake/Output section, or results review -> magnesium level, etc). Collection of this data will be initiated at the start of IRB approval and ongoing to completion. Full data analysis will be completed at conclusion of study followed by construction of manuscript. Of note, hypomagnesemia is corrected per standard ICU care with IV MgSO4 regardless of study, and liver transplant patients currently have a pre-designed magnesium replacement protocol (also used in our CVICU post-operative cardiac patients). This will still be included in data collection without adjustment to any comparison data in statistical analysis. This replacement protocol will not be used in our study as we will already be providing continuous IV MgSO4. Similarly, magnesium blood levels are checked independent of this study, although will be more frequent now for safety monitoring. These blood levels are drawn through a central line that is already in place independent of this study, so will not require percutaneous needle stick. There are no other drugs/devices involved in study or that would alter MgSO4 delivery.

*5.3.* Study Duration:

Experimental Group: Enrollment of study participants will be ongoing for entire duration of study as transplant becomes available. The total duration of participant participation will be approximately 1 week, however the length of time in the ICU is dependent on the overall post-operative transplant course, which can vary between patients. The duration anticipated to enroll all study participants is dependent on how long will be required to reach the targeted patient volume of 30, which will likely be approximately 3 years. The circumstances secondary to COVID-19 have made surgical schedules more unpredictable, and therefore a more confirmatory timeline is difficult to infer. Institutional scheduling of elective procedures and approval of patient enrollment did not occur until July 2020. Data analysis should not extend the study duration by more than 2-3 months.

Control Group: Control will be via retrospective chart review of same transplant population. Data analysis and manuscript preparation will follow (ideally with the project being fully concluded by May-June 2023). There is no intended long-term data follow up needed. Data analysis will be performed alongside experimental group data, and is not expected to extend the study duration by more than ~2-3 months.

*5.4.* Use of radiation*:* n/a

*5.5.* Use of Center for Magnetic Resonance Research*:* n/a

## 6. Data and Specimen Banking - n/a

## 7. Sharing of Results with Participants

*7.1.* Summary data from all participants will be created to acknowledge study participation and inform patients/parents of study conclusions once complete. No identifying information will be shared. Magnesium levels and overall pain requirements will be shared on daily family-centered rounds, however this is in accordance with standard information sharing with patients/families and is independent of research study.

## 8. Study Population

*8.1.* Inclusion Criteria: In order to be eligible to participate in this study, an individual must meet all of the following criteria:

Experimental Group:

1. Male or female of at least 3 years and <18 years of age at screening.
2. Written informed consent from participant's legal representative and assent (when applicable) obtained from participant and ability for participant to comply with the requirements of the study.
3. Stated willingness to comply with all study procedures and availability for the duration of the study
4. Be scheduled for and receive a liver transplant or total pancreatectomy and islet cell autotransplantation

Control Group:

1. Male or female of at least 3 years and <18 years of age at transplantation.
2. Received a liver transplant or total pancreatectomy and islet cell autotransplantation.

*8.2.* Exclusion Criteria: An individual who meets any of the following criteria will be excluded from participation in this study:

Experimental Group:

1. Pregnant or unwilling to abstain from sex if not practicing birth control during participation in the study.
2. Presence of a condition or abnormality that in the opinion of the Investigator would compromise the safety of the patient or the quality of the data.

3. Known allergic reactions to components of the MgSO4
4. History of heart block or myasthenia graves in past medical history.
5. Presence of cardiac pacemaker.
6. Age less than 3 years or greater than 18 years at screening.
7. Any patient with preoperative creatinine level > 1.5x upper limit of normal.
8. If study staff member not available for in-hospital presence on day of procedure.

Control Group:

1. Any patient who had filed as research-exempt (opt-out of research previously).
2. Age less than 3 years or greater than 18 years at transplantation.
3. Any patient with preoperative creatinine level > 1.5x upper limit of normal.

*8.3.* Screening: No specific screening measures will be used. Any transplant patient will be considered eligible if not pregnant. All consent/recruitment for the study is at same time as transplant procedural consent, which is performed by the transplant surgeon (whom is also a Co-Investigator on this study).

9. Vulnerable Populations

*9.1.* Vulnerable Populations:

| Population / Group | Identify whether any of the following populations will be targeted, included (not necessarily targeted) or excluded from participation in the study. |
|---|---|
| Children | Targeted Population |
| Pregnant women/fetuses/neonates | Excluded from Participation |
| Prisoners | Excluded from Participation |
| Adults lacking capacity to consent and/or adults with diminished capacity to consent, including, but not limited to, those with acute medical conditions, psychiatric disorders, neurologic disorders, developmental disorders, and behavioral disorders | Excluded from Participation |

| | |
|---|---|
| Non-English speakers | Included/Allowed to Participate |
| Those unable to read (illiterate) | Included/Allowed to Participate |
| Employees of the researcher | Excluded from Participation |
| Students of the researcher | Excluded from Participation |
| Undervalued or disenfranchised social group | Included/Allowed to Participate |
| Active members of the military (service members), DoD personnel (including civilian employees) | Excluded from Participation |
| Individual or group that is approached for participation in research during a stressful situation such as emergency room setting, childbirth (labor), etc. | Included/Allowed to Participate |
| Individual or group that is disadvantaged in the distribution of social goods and services such as income, housing, or healthcare. | Included/Allowed to Participate |
| Individual or group with a serious health condition for which there are no satisfactory standard treatments. | Included/Allowed to Participate |
| Individual or group with a fear of negative consequences for not participating in the research (e.g. institutionalization, deportation, disclosure of stigmatizing behavior). | Included/Allowed to Participate |

| | |
|---|---|
| Any other circumstance/dynamic that could increase vulnerability to coercion or exploitation that might influence consent to research or decision to continue in research. | Included/Allowed to Participate — though coercion will be adamantly avoided |

*9.2* Additional Safeguards:

Children: Entire targeted cohort will be a pediatric population <18 yo cared for in the PICU, where medical standards for care of pediatric patients are maintained and all attending level staff have degrees in pediatric intensive care or pediatric surgery. If a patient turns 18 while the study is ongoing, we will re-consent using an adult consent form. If a patient turns 18 while the study is ongoing, but is unable to consent for themselves (incapacitated), we intend for parental consent to stand until that participant became able to consent. Parental consent is described further in section 20.5.

Non-English Speakers: It is possible that family may be encountered which are non-English speaking, given the overall diversity in our area. Consent standards will be maintained in these cases with use of interpreter (in person, by phone, or by video), services which are provided by the University of Minnesota. We will include short form consent templates and a 2nd witness. Interpreters are also used for daily medical updates and on medical rounds, which is our current standard practice for all patients.

Illiterate: Consent forms will be read for the patient by research investigator with standard 'teach back' technique to ensure full understanding is obtained prior to informed decision-making. This aligns with standard of care and that used for consent for transplant surgery.

Military/Employees/Colleagues: While these populations are excluded given their age, children of any members of this population would be eligible for participation.

Undervalued or disenfranchised social group: Intention will be to offer IV $MgSO_4$ analgesia to all patients of all variety without any discrimination toward wealth, race, sexual identity or orientation, politics, social interests or preferences, stereotypes, or any other characteristic not mentioned in the exclusion criteria above.

Stressful Situation: Only anticipated situation for this study would be if patient develops acute disease exacerbation necessitating organ transplant (i.e. Liver). In

these cases patient and family are still given formal consent process prior to surgery. Consent for this IV MgSO4 use will be done at this time per protocol (i.e. no variance from the standard for other patients). Any unwillingness to discuss research protocol/consent due to stress will be immediately honored and patient excluded from study.

Disadvantaged: Intention will be to offer IV MgSO4 analgesia to these patients without any discrimination. Consent per routine protocol will be discussed without variance from the standard for other patients.

Serious Health Condition: Any patient which has developed a condition without any satisfactory standard treatments and has thus been offered transplant will still be considered eligible for this study. Consent per routine protocol will be discussed without variance from the standard for other patients. MgSO4 analgesia is independent of the underlying disease due to secondary pain from transplant.

Fear of negative consequences: Derived consent forms address our intent that participating or not participating has no bearing on consequences to patient regarding their care in the ICU. This will be discussed during the consent process without variance from the standard for other patients.

Increased vulnerability/coercion: There are no anticipated dynamics which would otherwise alter discussions of post-operative pain, which is a part of the initial transplant consent regardless. As for coercion, research investigators are also physicians directly involved in patient care. Dedication will be paid to patient autonomy as is for all patients. Consent will be obtained without variance from the standard for other patients.

None of the above populations affect the underlying physiology of post-operative pain and so seem appropriate to have all analgesic options discussed. Ongoing PICU research studies at the UMMC children's hospital are shared within the PICU physician group, so all are aware of any effects on medical care strategies. Emphasis on respect for patient autonomy will be made regarding decision for or against MgSO4 therapy in this communication. Additionally, this study's IV MgSO4 dosing will be built into the post-operative transplant care protocols which are shared with the medical team for each transplant patient. No one aside from the necessary treatment team is aware of medical management of these patients, so as to protect confidentiality and anonymity. These interventions should help prevent any undue harm to above populations.

## 10. Local Number of Participants

*10.1.* Local Number of Participants to be Consented: Local Number of Participants to be Consented: 30 consented for prospective cohort, 60 previous patients for control group. Assuming ~75% consent rate, this will require ~40 patients approached.

This number was originally determined based on power analysis performed on available literature - see section 15.2 (Power Analysis), however has been adjusted based on further stipulations during IND approval. Due to COVID alterations and other instigators on decreased procedures at this institution, this target may be altered to a lower number, with intentions to prove feasibility.

## 11. Local Recruitment Methods

*11.1.* Recruitment Process:

Experimental Group: Study team personnel will introduce this study at a patient's routine pre-operative PACCT appointment (pain specialist) for all TPIAT patients. This team is routinely involved in all TPIAT patients and is familiar with the post-operative analgesic course, and also presents an un-biased view in regards to this research. The transplant surgeon (Co-Investigator) will introduce this study at all Liver transplant patients' pre-operative visit while discussing analgesic management after surgery. It is possible that liver transplantation may be introduced as an emergent medical situation. Regardless, visits/discussions are done in private consultation. When available the co-investigator will be present for study introduction and consent as well. If the patient expresses interest, the TPIAT physician, transplant surgeon or co-investigator would introduce the details of study. Formal consent discussion will ensue if participant intends to enroll and will be supplemented from created consent/assent documents. Any signed documents will be uploaded to patient chart for adequate communication to treatment team. Similar procedure will be performed for liver transplant patients, however approach will be at a similar outpatient appointment with liver transplant team or while inpatient (if admitted for acute hepatic complications). Recruitment is intended to continue until the intended patient number is reached. Any patient contact, including if pre-admission consent is performed, will include adherence to COVID precautions per hospital guidelines. When it is not possible to obtain written informed consent for infection control or other justifiable reasons, we will use a waiver of documentation of written/signed documentation of consent and obtain phone consent from a parent or legal guardian and assent from the patient when deemed possible based upon patient age, developmental status and illness severity. Study coordinators will generally err on the side of utilizing the phone consenting process for infection control, unless the treating team allows for entrance into the patient's room. Study staff will create a consent narrative for each enrolled patient to document the consent process in detail.

Control Group: Participants will be identified from medical records

*11.2.* Identification of Potential Participants:

Experimental Group: Potential participants will be identified by the investigator from among patients under their care and that of their colleagues who have legitimate

access to their medical records. Potential participants will be asked about their interest in the study at the time of the pre-transplant visit.

All potential participants will be those that have become eligible for transplantation with our pediatric transplant surgeons. No other recruitment strategies will be used. The transplant surgeon (also a co-investigator of this study) will make initial contact with these patients/families, and will describe the intended treatment plan including consent for our study. The surgeon and PI will be in contact regarding each upcoming transplant patient that will be cared for in the PICU, in addition to consent and HIPAA authorization forms being added to patient chart so that can be confirmed at admission to the PICU.

Control Group: The records used in the study for the control group are the records of the patients in the investigators' clinical practices. Any medical records marked with the opt-out-research flag will not be viewed. A list of the past 60 patients based on inclusion criteria will be obtained from the BPIC at the UMN.

*11.3.* Recruitment Materials: n/a

*11.4.* Payment: n/a

## 12. Withdrawal of Participants

*12.1.* Withdrawal Circumstances: Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

1. Any clinical adverse event (AE), such as secondary toxic reaction to magnesium sulfate, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant. Specifics regarding secondary reactions:

   - regarding the hemodynamic adverse effects of magnesium: the drug will be halted for etiologic evaluation in the presence of confirmed hypotension or sustained bradycardia; if deemed secondary to magnesium that patient's therapy will be permanently discontinued
   - regarding sedative effects: the PICU team addresses sedation goals each day with rounds and follow up; preference with over-sedation will be to decrease other analgesia/sedative infusions as able given overall goal of this study (i.e. lower opioids, benzodiazepines, dexmedetomidine first as able). If deemed unable to decrease other infusions or already at a minimum, and over-sedation still present, then magnesium infusion will be discontinued.
   - regarding frequency of blood draws: blood draws are already frequent in this population of patients in initial 2 days post-op (typically every 6

hours at minimum already). If deemed by safety committee (familiar with typical transplant PICU course) that this population is suffering hemoglobin < 8 g/dL more frequently than is typical, and is not felt to be secondary to other complications from the surgery or transplant course, the patient's infusion will be stopped and the study will be halted to review the protocol and lab frequency further

2. Patient dosing is serially decreased to 0 mg/kg/hr per protocol
3. The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation, including if study staff member no longer able to be present in-hospital for OR check-in throughout procedure

*12.2.* Withdrawal Procedures: If a participant wishes to withdraw or we determine that the participant should withdraw, all data collected up to that point will be used in analysis unless the participant wishes for their data not to be used. We will intend for a partial withdrawal, where data will continue to be collected via private/protected records.

*12.3.* Termination Procedures: This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to investigator, funding agency, the IND sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension. The study team will notify the participants of the study termination. Specifically, the study will be halted if 2 patients develop clinically significant adverse reactions secondary to magnesium, at minimum until able to further review dosing and protocols. If arrhythmia (other than transient bradycardia), respiratory failure, or coma encountered once (also deemed secondary to magnesium), the study will be halted immediately with that patient until able to review with IRB and FDA. Per above, if encountering more frequent anemia than typical post-transplant course on multiple patients, the study will be halted to evaluate lab frequency's effect. The study will also be halted for further review if there is a dosing error.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

- Determination of futility.

The study may resume once concerns about safety, protocol compliance, and/or data quality procedures are addressed and satisfy IRB and FDA.

Data collected for the study prior to the study termination will be handled in the following manner:

- if the study is terminated due to safety reasons, the data related to AEs will be evaluated.
- if the study is terminated for any other reason, the regulatory and institutional document/data retention policies will apply.

## 13. Risks to Participants

*13.1.* Foreseeable Risks: This would include the potential for known side effects from magnesium toxicity, namely: hypotension, cardiac arrhythmia, hyporeflexia, effects on other electrolytes (such as potassium and calcium), muscle weakness, respiratory depression (secondary to muscle weakness), and increased sedation (including when combined with opioids and benzodiazepines). These toxic risks are cited typically at levels of > 4-4.5 mg/dL. We will minimize this risk by targeting magnesium thresholds below this. Hypotension is monitored for via routine serial blood pressure monitoring in all ICU patients, and can be treated with IV fluid resuscitation as needed (standard for hypermagnesemia treatment). Cardiac arrhythmia is monitored for via cardiac telemetry in all ICU patients, and cardiology specialists and arrhythmia resuscitation techniques are available per standard ICU care. Both of these are risk factors that are present in these populations regardless of magnesium use, however if these conditions are felt potentially contributed to by hypermagnesemia the infusion will be stopped for further evaluation. Electrolyte abnormalities are also common in ICU populations and are monitored routinely per post-transplant protocols. Respiratory depression is monitored routinely in this population as well, however if secondary to perceived muscle weakness out of proportion to standard post-operative course, the magnesium infusion will be stopped as well. Sedation and other analgesia is routine in post-operative transplant care and is addressed and titrated based on daily goals. Decreasing other sedatives will take precedent over magnesium in cases of oversedation given the overall objective of the study. Increased blood draws may occur during monitoring, however in 48 hours of infusion may result in only 4-8 mL of extra blood specifically from magnesium draws alone, which clinically seems insignificant relative to overall course. There is potential for dosing error as is for all PICU delivered medications, however correct units for MgSO4 has been updated in UMMCH pump library, and there is additionally standard ICU regulations per institutional and leadership for routine drip/dose checks. The only other potential foreseeable risk would be that of intravenous line capability. Post-operative transplant patients require multiple IV

medications (both bolus and drips), which sometimes require placement of additional IV catheters. Given that magnesium is already periodically replaced in these populations for hypomagnesemia, we think the risk for impacting line availability is rather low, but in theory could increase potential of line complications. IV catheter complications are anticipated/potential risks of any patient in the ICU independent of this study. Per the above protocol, there will be both peripheral and central line magnesium concentrations in case there are compatibility issues where magnesium cannot be administered in the same IV line as another medication (amphotericin and calcium infusions being the two rare instances that could occur). Risk for administering the wrong concentration into its intended IV line (peripheral or central) will be avoided via separate Epic orders ('PERIPHERAL' and 'CENTRAL' built into the research medication entry), appropriate labeling and delivery by the IDS, pharmacy checks (routine on all ICU administered medications), and nursing checks (also routine standard of care). All efforts will be made to protect participants' confidentiality following Good Clinical Practice, the policies of the Committee on Clinical Investigations (IRB), and Federal and State laws as they apply. There is risk of protocol deviation. This will be mitigated by routine IRB evaluations, study staff check-in communication with PICU providing teams and study staff presence in OR on day of procedure.

*13.2.* Reproduction Risks: n/a

*13.3.* Risks to Others: no perceived risk to others

## 14. Potential Benefits to Participants

*14.1.* Potential Benefits: The most notable potential benefit to study participants is for a more comfortable ICU stay with less opioid requirement. This would hopefully correlate with less overall opioid side effects, which otherwise may further contribute to morbidity (most notably constipation, ileus, itching, nausea). It is difficult to predict the likelihood of this impact given lack of data in this population, however the potential for beneficial effect of an otherwise physiologically required electrolyte compared to minimal chance of side effect seem an optimal opportunity for study. If proven beneficial, the magnitude may be quite significant, with the potential to alter protocols in these populations, and further fuel studies regarding magnesium's analgesic effect and dosing optimization. While we anticipate that our impact on these children will mostly be in the ICU, adult patients have more notable long-term opioid requirement (something not as replicated in kids according to TPIAT studies), and may be an interesting new cohort to study as well given overall opioid burden nationwide.

## 15. Statistical Considerations

*15.1.* Data Analysis Plan: EPIC will be the source document used for collection of all data, which will be transferred to REDCap for clinical database. The following will

be the data collected from epic for statistical analysis. No data is associated with any specimens or printed material. These measures are also provided as a list in an attachment for ease of use.

***PRIMARY OUTCOMES***

Total opioid usage

1. Morphine Equivalents for OR, PICU, and overall course (total dose/kg/day)
   - use MAR to determine which opioid using: morphine, hydromorphone, fentanyl, oxycodone, or methadone
   - use summary -> index -> pain monitoring tab to evaluate 24 hr infusion requirements; days are considered 7am-7am; this tab will be used for other data collection below
   - confirm infusion dosing adjustments in MAR (hover over green time bars)
   - we will use guidance from our PACCT team (pain specialist) and available literature for equianalgesic dosing conversions (i.e. fentanyl to morphine, hydromorphone to morphine, etc)
   - divide by weight (kg) for morphine equivalent per kg

***SECONDARY OUTCOMES***

opioid variables

1. Morphine Equivalent daily variance (daily dose/kg on each post-op day)
2. Total days on IV opioids
   - will use post-operative day when IV opioid discontinued (i.e. POD#6)
3. Total days on any opioid
4. PCA variables
   - # of demands, # of deliveries (daily and total values)
   - # of escalations in infusion dose
5. Scheduled vs PRN dosing
   - scheduled dosing includes PCA infusion dose and scheduled IV or PO opioids
   - PRN includes PCA delivered doses and PRN opioids delivered

Opioid side effect variables

1. Constipation
   - # of ileus events — search ileus in epic search tool
   - days until first stool — will use first post-operative day which stool documented (i.e. POD#3)
   - total stools, stools/day
   - enema use
2. Nausea
   - # emesis (daily and total per day)
   - # anti-emetic doses (including Zofran, Compazine, granisetron, Benadryl, lorazepam, cyproheptadine, scopalamine; daily and total per day)
3. Itching
   - # days naloxone infusion required

4. Respiratory Variables
   - # escalations required
   - Peak respiratory requirement each day
   - # Days intubated

Other pain/comfort variables

1. FLACC, Pain Score (self-reported), comfort B scores - daily and total/day
2. PICU duration — post-operative day when transfer order placed (i.e. POD#7)
3. Intubation
   - # of days intubated — will track as earliest post-operative day extubated (i.e. POD#1)
   - # of re-intubations
4. Paravertebral Block — whether used (yes or no), # of times dose increased
5. Ketamine use — total mg/kg, mg/kg/d
6. Total doses and doses/day: Acetaminophen, Ketorolac, ibuprofen, celecoxib, gabapentin, amitriptyline
7. Dexmedetomidine — total mg/kg, mg/kg/day, peak dose
8. Midazolam – whether infusion required each day
9. PT involvement (# successful visits, POD# at initiation)
10. Feeding Advancement (day at initation, day at goal feeds)

***SIDE EFFECTS AND MISCELLANEOUS***

Magnesium variables

1. Magnesium levels
   - average daily level (for each post-operative day), average total level
   - peak level during admission
2. Dosing
   - # of magnesium infusion dosing changes (i.e. # times decreased)
   - total days on magnesium (POD# at discontinuation
   - # times held due to adverse event concern
   - # of adverse events deemed secondary to magnesium
   - type of adverse event
3. OR Effect
   - Time spent bradycardic (value and %)
   - Overall OR time
   - Fluid requirement
   - Blood product requirement
   - Pressor variables (# required, peak doses)
4. Other effects
   - ionized calcium levels — average daily level (for each post-operative day) and average total level
   - potassium levels — average daily level (for each post-operative day) and average total level
   - phosphorous levels - average daily level (for each post-operative day) and average total level

- PTH level (for renal patients where relevant)
- creatinine levels (average daily and average total; part of routine monitoring of all transplant patients)

Standard Reporting

2. type of transplant received
3. age
4. weight
5. height
6. gender

*15.2.* Power Analysis: Power analysis was performed based on pediatric studies by Hutchins et al and Jabbour et al (see references section 24), indicating 90 patients in order to see a detectable difference of 20% between study groups with 80% power. This would detect a decrease of nearly 3.5 mg/kg over a 7 day PICU course, and seemed a reasonable target for our hypothesis. Given the progression of IND review, this number will be reduced to 60 for the retrospective cohort (renal transplants removed from study), and 30 for prospective cohort (typical target for pilot-based study), to simulate a pilot study rather than fully correlational study. Regardless, original power analysis is shown below:

| | Detectable difference between groups (Total 1st 7 days in morphine equivalent mg/kg) | | Detectable difference between groups (% reduction in dose) | |
|---|---|---|---|---|
| n per group | 80% power | 90% power | 80% power | 90% power |
| 40 | 5.26 | 6.09 | 29 | 33 |
| 50 | 4.70 | 5.43 | 26 | 30 |
| 60 | 4.28 | 4.95 | 24 | 28 |
| 70 | 3.96 | 4.58 | 23 | 26 |
| 80 | 3.70 | 4.28 | 21 | 24 |
| 90 | 3.49 | 4.03 | 20 | 23 |
| 100 | 3.30 | 3.82 | 19 | 22 |
| 110 | 3.15 | 3.64 | 18 | 21 |
| 120 | 3.01 | 3.49 | 18 | 20 |

Based on a pooled SD estimate for total morphine equivalent dose first 7 days post-op of 8.3 mg/kg (Hutchins 2016), the table lists the minimum differences (in mg/kg) that are detectable with 80% and 90% power for various enrollment sizes. These differences are also presented in terms of the % reduction in total dose, based on an overall mean total dose of 15.5 mg/kg (Hutchins 2016). For comparison, a 29.5% reduction in total dose (first 48h) in ketamine + magnesium versus ketamine was observed in Jabbour 2014.

*15.3.* Statistical Analysis: The primary analysis will compare the total morphine equivalent dose per kg during the PICU stay between experimental and historical control groups. Total dose will be compared in both unadjusted analyses and adjusted analyses using linear models, with a covariate for study group and adjusting covariates for transplant type, age, and gender, to account for potential variation due to these factors. Distributional assumptions will be examined and data transformations will be used as appropriate. Secondary outcomes will be compared using similar approaches using generalized linear models for count

outcomes (total days on IV opioids, number of PCA demands and deliveries, number of infusion dose escalations, number of ileus events, days until first stool, emesis counts, number of days naloxone infusion required, PICU duration, number of days intubated, paravertebral block dose increases), categorical outcomes (ketamine use, presence of side effects), and continuous outcomes (FLACC, Pain Score). Longitudinal measurements of magnesium, other analgesics, ionized calcium, PTH, and creatinine levels will be analyzed using mixed effects models. Group summaries including means, standard deviations, and rates will be reported and group differences will be summarized as incidence rate ratios, odds ratios, or mean differences with 95% confidence intervals. Analyses will be conducted using the intent-to-treat principle; control group participants who underwent magnesium replacement (for hypomagnesemia or pre-designed post-transplant protocol) will be included in the control group, and experimental group participants with discontinuation of magnesium, if any, will be included in the experimental group. A two-sided 5% level result will be regarded as significant. Statistical analysis will be per statistician's updated STATISTICAL ANALYSIS SOFTWARE (also used in a previous pain study with TPIAT cohort).

*15.4.* Data Integrity:

Data collection is the responsibility of the clinical study staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the study. All paper data (which would include only consent/assent forms) will be kept in a dedicated, locked, research space, in co-investigator's office at UMN Children's Hospital. Other source data will be stored in EPIC. Consent and assent forms will be transitioned to the patient chart upon completion. Paper copies of these forms will be stored in a locked storage bin in co-investigator's office at UMN Children's Hospital.

Protocol with study schedule and patient enrollment will be tracked with OnCore programming. Electronic data collected from the PICU admission will be stored on REDCap program as a clinical database, a secure environment delivered by the Center of Excellence for HIPAA Data intended for storing, sharing and accessing sensitive and private highly restricted files.

Data access will be limited to research assistant, research coordinator, statistician support, and key study personnel (PI and co-investigators).

Upon completion of project, the master data matrix and patient identification key will be destroyed.

## 16. Health Information and Privacy Compliance

*16.1.* Select which of the following is applicable to your research:

☐ I am requesting that all research participants sign a HIPCO approved HIPAA Disclosure Authorization to participate in the research (either the standalone form or the combined consent and HIPAA Authorization).

Appropriate Use for Research: Per language in the consent at initial procedural discussions with the surgeon, unless consenting to enroll for magnesium analgesia, patients will not be involved in any research protocol. MRN's will not be forwarded to IDS or protocol team to initiate any form of data collection or medication administration.

*16.2.* Identify the source of Private Health Information you will be using for your research (Check all that apply)

☐ I will pull records directly from EPIC.

*16.3.* Explain how you will ensure that only records of patients who have agreed to have their information used for research will be reviewed: Patients who have consented for the study will have their information shared with the research team. Patient information is updated in RedCap. Only patients enrolled in study will have RedCap entries, which will be the only patients whose Epic charts will be accessed for further data collection.

*16.4.* Approximate number of records required for review: 60 retrospective records (30 liver transplant, 30 TPIAT), 30 prospective. Informatics consulting service will be utilized, however certain data may require more thorough progress note analysis and therefore direct epic access from data reviewer.

*16.5.* Please describe how you will communicate with research participants during the course of this research. Check all applicable boxes

☐ Communication with research participants will take place in the course of treatment, through MyChart, or other similar forms of communication used with patients receiving treatment. Specifically, communication will happen throughout their PICU course regarding their overall care, which will include discussions on analgesia and sedation to ensure these are optimized (this happens during family-centered rounds on all patients admitted to the PICU).

*16.6.* Explain how the research team has legitimate access to patients/potential participants:

Members of the research team are also part of the PICU team involved in patient care, and therefore will have access to medical records independent of this project (PI is a PICU attending physician, co-investigators are transplant surgeon and PICU fellow physician). A medical student will also be assisting in data collection as part of their research experience. All members have been confirmed to have completed appropriate HIPAA and research training through UMN standards. Access to patient charts is discussed during the consent process with patients. A number of data points require manual searching in epic. None of these data points require demographic or personalized information outside of sex, age, and strictly medical information (name and contact information are ignored for example).

*16.7.* Location(s) of storage, sharing and analysis of research data, including any links to research data (check all that apply).

☐ In the data shelter of the Information Exchange (IE)

☐ Store ☐ Analyze ☐ Share

☐ In the Bone Marrow Transplant (BMT) database, also known as the HSCT (Hematopoietic Stem Cell Transplant) Database

☐ Store ☐ Analyze ☐ Share

☒ In REDCap (recap.ahc.umn.edu)

☒ **Store** ☒ Analyze ☐ Share

☐ In Qualtrics (qualtrics.umn.edu)

☐ Store ☐ Analyze ☐ Share

☒ In OnCore (oncore.umn.edu)

☒ **Store** ☒ **Analyze** ☐ Share

☐ In the University's Box Secure Storage (box.umn.edu)

☐ Store ☐ Analyze ☐ Share

☐ In an AHC-IS supported server. Provide folder path, location of server and IT Support Contact:

☐ Store ☐ Analyze ☐ Share

☐ In an AHC-IS supported desktop or laptop.

Provide UMN device numbers of all devices:

☐ Store ☐ Analyze ☐ Share

☐ Other. Describe:

Indicate if data will be collected, downloaded, accessed, shared or stored using a server, desktop, laptop, external drive or mobile device (including a tablet computer such as an iPad or a smartform (iPhone or Android devices) that you have not already identified in the preceding questions

☐I will use a server not previously listed to collect/download research data

☐I will use a desktop or laptop not previously listed

☐I will use an external hard drive or USB drive ("flash" or "thumb" drives) not previously listed

☐I will use a mobile device such as an tablet or smartphone not previously listed

*16.8.* Consultants. Vendors. Third Parties. N/A

*16.9.* Links to identifiable data: MRN's will be uploaded securely into RedCap, there will be no other links or substitute identifiers required.

*16.10.* Sharing of Data with Research Team Members. Data will be stored via RedCap and OnCore programming only.

*16.11.* Storage and Disposal of Paper Documents: There are no anticipated paper products other than signed consent/assent forms, which will be stored in a secure, locked storage box in co-investigator's fellow office on UMN Children's Hospital grounds.

## 17. Confidentiality

*17.1.* Data Security: All members of the investigation team will complete and maintain university standard training programs regarding patient information protection, including all modules provided at initiation of fellowship. As stated, this will be extended to medical student researcher involved with assistance in chart review. Protocol, study schedule, and patient enrollment will be tracked via OnCore. Various outcome measures collected from the Epic EMR will be transferred to REDCap storage system. Both of these are HIPAA compliant. This system is password-protected and encrypted for security. Consent forms will be stored in patients' medical chart, with the purpose of easy retrieval and access for PICU medical staff to initiate the intervention following transfer from operating room. This will be reflected in the confidentiality section of the consent form. Paper copies of consent/assent forms will be stored in a secure, locked storage box in co-investigator's fellow office on UMN Children's Hospital grounds.

## 18. Provisions to Monitor the Data to Ensure the Safety of Participants

*18.1.* Data Integrity Monitoring: The PI and co-investigators will be in direct day-to-day contact (specifics below) throughout the study intervention and with any of the following that arise. The PI and/or co-investigator will have direct notifications any time a transplantation surgery is planned and will confirm that study intervention has been ordered correctly in medical chart on day of PICU admission. Surgery, anesthesia, ICU, and safety monitoring teams will be notified prior to interventions when a patient is confirmed as a study participant. Medical staff will be instructed to page PI and/or co-investigators as well as research coordinator in case of any intervention side effect for further direction. The PI and co-investigators are the most appropriate direct monitors, as both have full understanding of research protocol, and are also frequently in PICU with direct care of these patients. In cases where the PI or co-investigators are not present, deferral will be made to the medical team, which is already adept and required to be following lab results and ensuring nurse orders are carried out. A co-investigator will also otherwise make routine daily lab surveillance for added layer of monitoring. This level of monitoring appears appropriate as once the intervention is ordered in our EMS, nurses carry out the order throughout duration of study. There is no blinding required in this study as all participants will be intended to receive intervention, so there appears no opportunity for bias introduced by the PI or co-investigators while caring for these patients. As patients complete their ICU and conclude their involvement in study, chart reviewer will be notified to update data into REDCap. This will be further overseen by PI and co-investigators. All data collected through chart review will be collected with a standardized data collection form to ensure uniformity.

Specific safety measures to prevent protocol non-compliance include the following: study team will have a brief after enrollment of each patient and prior to infusion initiation to review pertinent protocol elements, which will be debriefed to medical team (both in email and in person); a study team member will check-in with medical team and bedside nursing team twice per day to ensure compliance and answer any questions; a study team member will check in at major checkpoints (specifically at dosing change and at discontinuation); there will be a request for nursing to be calling study team at medication discontinuation for added layer of safety; a study member will be available for contact from care providers at all times; only study team members are able to direct order changes in epic pertaining to $MgSO_4$ dose or frequency of level checks, resident physicians specifically are not to change these orders (medical team attending or fellow physicians may change dosing per protocol if level > 3.5 mg/dL); study team will additionally contact both bedside nursing team and medical team following completion of infusion to review current safety profile (specifically lab trends, infusion dosing, appropriateness of timing, and active problem list to ensure no adverse events secondary to $MgSO_4$). In regards to OR

safety, a study staff member will be specifically in-hospital on the day of procedure. This staff member will go to the OR every 2 hours at the time magnesium levels are drawn to provide a helpful reminder of blood draw requirement, ask if there are any questions regarding the study drug, and help address any new concerns. Data regarding magnesium levels (and all labs) as well as intra-operative vitals (such as heart rate and blood pressures) and medication deliveries/changes are auto-populated into the patient's electronic medical record in real-time. We do not anticipate that the anesthesia team should have to report any additional data for the study team to help guide dosing magnesium dosing adjustments. The study team member will follow up the result of this level. If there is a needed dosing change based on the level, that study team member will return to the OR to provide a helpful reminder to change the dose (in the case this has not yet been done). If the anesthesia provider is too busy to draw a level or change the dose, which is not anticipated, study team will seek out an available anesthesiologist (i.e. on call provider) to come pause the infusion until able to further discuss. If a study staff member is not forecast to be available for day of procedure, that patient will be excluded from consent. If a study staff member becomes unavailable on day of procedure, that patient will be removed from the study.

A data integrity monitor (external to the direct research team) will be involved throughout this project. The study monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements. The monitor will provide ongoing monitoring of data validity and regulatory issues (e.g. eligibility determinations, consent form process, SAE reporting, IRB actions, disclosures of conflict of interest).

Study records will be monitored at regular intervals by the study monitor. The monitor will perform source data verification and as such must be given access to the participant's primary source documentation, such as paper or electronic medical records, consent to participate in the study, visit dates, demographic information, medical history, physical examination, vital signs, copies of laboratory reports, AEs, concomitant medications, drug accountability (etc.), that support data entries in the REDCap database.

The PI will be provided copies of monitoring reports shortly after the monitoring visit. Findings will be noted and followed up in the subsequent monitoring visit.

The study will be monitored by CTSI in accordance with its institutionally approved monitoring plan.

*18.2.* Data Safety Monitoring: The following safety data will be collected starting at the baseline visit through the end of study visit to establish any change from baseline parameters, and for monitoring adverse events:

- Confirm that participant met inclusion/exclusion criteria
- Confirm that delivered magnesium dose is appropriate with intended protocol dosing (i.e. 50 mg/kg bolus, 15 mg/kg/hr infusion)
- hypotensive events: including value and interventions needed (pressors, fluid bolus, etc)
- respiratory decline: specifically if needing to increase to higher level of support (nasal cannula to high flow, high flow to positive pressure, etc), interventions required for respiratory compromise, relation to sedation
- arrhythmia: include type, EKG results (if done), interventions required
- hypocalcemia: specifically if ionized calcium < 4 (or age-appropriate norm), interventions required
- hyperkalemia: include value (if higher than normal range), interventions required
- hyperphosphatemia: include value (if higher than normal range), interventions required
- hypermagnesemia: include if > 3.5, confirm that dose was decreased per protocol guideline
- for all of above, comment on whether side effects deemed secondary to magnesium

Safety data will be captured in the CRFs for each visit. Any AEs and SAEs will also be recorded in the REDCap database. Any safety event meeting the IRB's urgent reporting criteria will be reported to the IRB within its published timelines, and similarly to the FDA as outlined at conclusion of this section.

A pediatric ICU physician external to the research team will serve as the safety monitor for this protocol. The safety monitor will not be enrolling any research participants or caring for patients as part of this protocol. The safety monitor is qualified to review the patient safety data generated by this study because of her/his expertise in pediatric intensive care.

After the first 3 patients have completed their study duration, the safety monitor will be responsible for reviewing adverse events and participant data for any clinically significant trends, followed by providing a short one page summary regarding findings. Safety data collected will include the above list, as well as any other unforeseen events which are deemed potentially secondary to magnesium. As long as meeting safety

efficacy, the data and adverse event review will be completed after every 5 patients for duration of the study, unless any clinically relevant items deem alteration of these review intervals. Any serious or unexpected events will be thoroughly investigated followed by a short report independent of the above 3 and 5 patient review intervals. PI is responsible for notifying safety monitor via telephone or email of any events within 1 day that she or trial team are made aware.

We do not predict any adverse events to occur at our protocol dosing based on available literature. If a SAE, Unanticipated Problem Involving Risks to participants or Others (UPIRTSO) or other event causing risk to the research participants occurs, the clinical research team will notify safety monitor immediately. Safety monitor will assure the study is conducted in accordance with the investigator's agreement, the investigational plan, the IND and other applicable FDA regulations, and conditions of approval imposed by the reviewing IRB or FDA. Research will be suspended immediately if any life-threatening events occur due to magnesium.

An Annual Report will be compiled by the research team and will include a list and summary of AEs. In addition, the Annual Report will address (1) whether AE rates are consistent with pre-study assumptions; (2) reason for dropouts from the study; (3) whether all participants met entry criteria; (4) whether continuation of the study is justified on the basis that additional data are needed to accomplish the stated aims of the study; and (5) conditions whereby the study might be terminated prematurely.

The Annual Report will be sent to the safety monitor and will be forwarded to the IRB and FDA. The IRB and other applicable recipients will review progress of this study on an annual basis.

Below outlines definitions and specifics regarding relevant events:

# Safety and Adverse Events

## *A. Definitions*

***Adverse Event***

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries will be regarded as adverse events, whether or not considered intervention-related. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms

- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

***Classification of an Adverse Event***

Mild: Events require minimal or no treatment and do not interfere with the participant's daily activities —— Moderate: Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning. — — Severe: Events interrupt 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".

Of note, we do not intend to report mild side effects which are known to frequently occur in TPIAT and Liver transplants. For example, we will not report individual episodes of nausea/emesis, post-operative pain, ventilator adjustments (unless an escalation to new mode of respiratory support), non-sustained hypertension/hypotension on routine vital checks, anticipated returns to OR (for example to close abdomen after initial surgery). Similarly, known/predicted intraoperative fluctuations in coagulopathy, bleeding, and vitals trends will not routinely be reported, unless not responding to expected interventions per OR team. All of the above will be reported if medical team experts (i.e. surgeon or anesthesiologist in OR, intensivist in PICU) believe these above symptoms are contributing to an atypical course or a worsening in patient's expected trajectory.

***Relationship to Study Intervention***

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and her/his clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

Probably related: There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition. —— Possibly Related: There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate. —— Not Related: The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

***Serious Adverse Event***

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs a hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event based on appropriate medical judgment or that requires medical or surgical intervention to prevent one of the above outcomes listed in this definition

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

### *Adverse Event Reporting Period*

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 7 days following the last administration of study treatment or until discharge from the ICU (whichever occurs first).

### *Preexisting Condition*

A preexisting condition is one that is present at the start of the study. A preexisting condition will be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

### *General Physical Examination Findings*

At screening, any clinically significant abnormality will be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event will also be recorded and documented as an adverse event.

### *Post-study Adverse Event*

All unresolved adverse events will be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator will instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

### *Hospitalization, Prolonged Hospitalization or Surgery*

Any adverse event that results in hospitalization or prolonged hospitalization will be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

## *B. Recording of Adverse Events*

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document (i.e. within 24 hours of event notification), and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results will be recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

## *C. Reporting of Serious Adverse Events*

### 1. IRB Notification by Investigator

Reports of all serious adverse events (including follow-up information) must be submitted to the IRB within 5 working days if it falls under the UPIRTSO guidelines. Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's binder.

### 2. FDA Notification by Sponsor

The study sponsor shall notify the FDA by telephone or by facsimile transmission of any unexpected fatal or life-threatening experience associated with the use of the drug as soon as possible but no later than 7 calendar days from the sponsor's original receipt of the information.

If a previous adverse event that was not initially deemed reportable is later found to fit the criteria for reporting, the study sponsor will submit the adverse event in a written report to the FDA as soon as possible, but no later than 15 calendar days from the time the determination is made.

| Agency | Criteria for Reporting | Timeframe | Form to Use | Submission address/fax numbers |
|---|---|---|---|---|
| U of MN IRB | SAE: fatal, life-threatening or serious, unexpected, at least possibly related | 5 working days | MedWatch 3500A Form | RNI in ETHOS |
| FDA | SAE: fatal, life-threatening, unexpected, at least possible related | 7 calendar days | MedWatch 3500a Form but alternative formats are acceptable (e.g. summary letter) | Fax: 1 (800) FDA - 0178 |
| | SAE: serious, unexpected, at least possibly related | 15 calendar days | | |

## 19. Provisions to Protect the Privacy Interests of Participants

*19.1.* Protecting Privacy: Patients will be given opportunity in initial consent process as to whether there are any members of medical or research team they wish to interact or not interact with, desires which will be maintained. The only members which should have direct contact, however, will include the PI and co-investigators (if on medical staff). Autonomy will be emphasized to all members of research team, including transplant surgeon (co-investigator) or PACCT physician performing initial consent, with respect for any patient who wishes not to enroll in our intervention. This will be emphasized to medical team involved in PICU care of patients as well. We do not otherwise anticipate any privacy concerns as our intervention is not dependent on any other underlying attributes other than the transplantation procedure itself. HIPAA compliance measures are otherwise routine at the institution where study is taking place. Comorbidities and transplant indication will not be identified in either control or experimental group, which should further limit potential of identifying information in final written product.

*19.2.* Access to Participants*:* The research team will need access to medical chart in order to collect data regarding the primary and secondary outcomes, as this is the

only place data is stored/located. We will only search chart in specific areas that our outcome measures are located, and will avoid all other unnecessary information. Some of the data elements need more diligent, subjective searches than what can be consistently and reliably obtained by computer data extraction techniques (which were discussed during development process). Specifically, the EMR will be accessed for appropriate patient by MRN, followed by selecting the appropriate surgical encounter, followed by only specific portals in epic where intended data elements are located (i.e. Intake/Output or results review -> magnesium level, etc). The PI and co-investigators, however, will have more frequent and expanded access to chart in circumstances where they are the medical provider taking care of patient for the day (unrelated to research itself), since that person may be directly involved in patient care. All of the patients are otherwise within the co-investigator's (transplant surgeon) and PI's (PICU physician) practice area.

## 20. Compensation for Research-Related Injury

*20.1.* Compensation for Research-Related Injury: In the event that research-related activities result in an injury, treatment will be provided to the participant (e.g., first aid, emergency treatment, and follow-up care as needed). Care for such injuries will be billed in the ordinary manner to the participant or the participant's insurance company.

*20.2.* Contract Language: n/a

## 21. Consent Process

*21.1.* Consent Process (when consent will be obtained):

Experimental Group: consent will be obtained, before any research procedure occurs, in the initial meeting between the transplant surgeon (co-investigator) or PACCT physician and parents (with or without patient) when discussions regarding their procedure are had. This is done in a private setting, though dependent on situation (i.e. surgeon office, hospital conference room if more emergent, etc). Parents will be given opportunity to address questions per usual routine, and will use standard 'teach back' technique to elicit understanding from parents. Written consent will be obtained and stored in patient chart. If a liver transplant candidate develops more acutely, consent will be attempted while inpatient prior to any procedure initiation. Any patient contact, including if pre-admission consent is performed, will include adherence to COVID precautions per hospital guidelines. When receiving consent/assent over the phone, study staff will hand a copy of the consent, HIPAA and assent if applicable through a small door on the side of the patient's room. There will be another study coordinator on the phone via conference call to witness/attest to the consent process. Study staff will create a consent narrative not to file for each enrolled patient to

document the consent process in detail which will be signed by both the consenting coordinator as well as the coordinator serving as the witness.

Control Group: we intend for a waiver of consent for data review of control group given both that treatment was at an academic institution and information will be de-identified.

*21.2.* Waiver or Alteration of Consent Process (when consent will not be obtained): There will be no waiver or alteration of consent process for the experimental group. We intend for a waiver of consent for the retrospective control group. The control group of this research is not FDA-regulated as patients were given standard of care treatment. No investigational drug was given to these participants. The research does not involve non-viable neonates. The research does not involve newborn dried blood spots. The research could not practicably be carried out without a waiver. For the control group, the research involves no more than Minimal Risk to the participants. The waiver will not adversely affect the rights and welfare of the subjects.

*21.3.* Waiver of Written/Signed Documentation of Consent (when written/signed consent will not be obtained): n/a

*21.4.* Non-English Speaking Participants: non-english participants are likely over the course of the study. Participants who do not speak English may be enrolled. Consent short forms will be used for those participants who will not be able to understand the consent form written in English. The short form will be used in conjunction with an oral presentation of the consent information by a translator. We will make use of in-person interpreters through the UMN's extensive interpreter service for any participants whom English is not preferred language. An impartial witness who is fluent in both English and the language spoken by the participant/representative will be present during the entire consent discussion to attest to the adequacy of the consent process and to the participant's voluntary consent. The interpreter may serve as a witness.

*21.5.* Participants Who Are Not Yet Adults (infants, children, teenagers under 18 years of age): all patients will be consented or assented (if age 8-17 years) in accordance with HRP-013 and Minnesota state regulations. We anticipate all of our patients to be under 18 years old and therefore children. In the rare event that children are emancipated, we will consider legal council if unclear. Registration of these patients confirms guardianship and so will determine appropriate person to consent. Consent is required by 1 parent (research is greater than minimal risk with the potential of benefit). Discussions will be provided regarding pain control in children, and assent will be allotted to those at least 8 years old. Any patient contact, including if pre-admission consent is performed, will include adherence to COVID precautions per hospital guidelines. When entering the room isn't reasonable due to infection risks, assent

will be obtained over the phone with the parent also on the call (i.e., either in the room with the patient or conference called into the phone so that they are able to hear their child's questions, concerns, and response to participating).

*21.6.* Cognitively Impaired Adults, or adults with fluctuating or diminished capacity to consent: per above consent process, if a patient turns 18 while study is ongoing, and does not have capacity to consent, consent will be deferred to parent.

*21.7.* Adults Unable to Consent: n/a

## 22. Setting

*22.1.* Research Sites: All research will be conducted in the PICU at the University of Minnesota Masonic Children's Hospital located at 2450 Riverside Avenue in Minneapolis, Minnesota. Recruitment may occur at a private UMN setting during the initial consent for transplantation if this occurs outpatient (i.e. for TPIATs primarily). This will primarily occur in the transplant physician (co-investigator) office or TPIAT physician's office, as outlined in consent sections. For inpatient settings required in the PICU, consent will preferentially occur in a family conference room.

*22.2.* International Research: n/a

## 23. Multi-Site Research: n/a

## 24. Coordinating Center Research: n/a

## 25. Resources Available

*25.1.* Resources Available: PI and co-investigator have multiple other research colleagues available for assistance if needed. As stated above, it is difficult to predict how many potential participants we will have since transplant is a dynamic field year-to-year, but based on previous years we predict ~10-20 patient per year. The co-investigator (PICU fellow) is allotted multiple blocks each year to research, so most of this time will be devoted to conducting and completing our project, including following up on chart review progress, additional external grant applications, manuscript writing. Multiple other members will also be assisting with various tasks, including a research coordinator who will help with database creation (OnCore and REDCap) and ongoing study monitoring. Data integrity and safety monitoring members are available through UMN services. Biostatistician will be hired through grant funding for data analysis. We anticipate that the combination of these contributors will be enough resource for the project. The UMN Masonic PICU is a 24-bed unit with capability for all current standard-of-care modalities needed in critical care. PI has a fellow office where able to review research data privately. Patients have access to various therapies (PT/OT/ST, music therapy) for their

care, as well as all common pediatric specialties within the UMN system should consultation be needed - including psychological. PI and co-investigator will plan for cumulative update meetings with research team no less than every 6 months. We do not anticipate clinical service from medical team to be burdened by any of the protocol interventions, and project will be discussed with unit manager.

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**General Review**

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