# Title: A Randomized Trial Evaluating Use of Long-Acting Liposomal Bupivacaine (Exparel®) in Reducing Narcotic Pain Requirements in Patients Undergoing Minor Urologic Procedures

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# JHM IRB - eForm A – Protocol

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## 1. Abstract

a. Provide no more than a one-page research abstract briefly stating the problem, the research hypothesis, and the importance of the research.

This research proposal aims to evaluate the utility of long-acting liposomal bupivacaine (Exparel®) in improving pain scores and reducing narcotic pain requirements in pediatric patients following minor urologic procedures. One means of reducing postoperative opioid requirement is use of local anesthetic medications at the time of surgery. Exparel® is an FDA-approved long-acting bupivacaine formulation that allows retention of local anesthetic at the site of injection to allow for durations as long as 72 hours. Currently, there is wide variation in practice patterns regarding use of intraoperative local anesthetics and postoperative narcotic pain medication following pediatric urologic procedures. A recent study from two large academic centers demonstrated that that nearly all patients (96%) undergoing circumcision, inguinal orchiopexy, or hydrocele/hernia repair were prescribed opioid analgesia. Post-discharge opioids were prescribed in higher quantities to the very young (age 0-2 years) followed by the older population (age >10 years).[1] In addition, there was significant variability in opioid prescribing patterns between attendings and trainees, amongst individual providers, and across institutions. One consequence of high opioid prescribing in this patient population is leftover opioid medication in the household. One study found that over two-thirds of patients had greater than 75% of their opioid medication leftover, and only about 10% of families properly disposed of these opioid medications.[2] Given the lack of standard practice and implications for patient safety, we propose a randomized controlled trial to evaluate the impact of combination long-acting liposomal bupivacaine (Exparel) plus standard 0.25% Marcaine on improving pain scores and reducing narcotic pain requirement when compared to standard 0.25% Bupivacaine (Marcaine) alone. Patients will also be cross-randomized to receive standard postoperative pain instructions with or without opioid disposal instructions to demonstrate whether inclusion of these materials improves the rate of opioid disposal after these medications are no longer needed (already being separately evaluated as a QI initiative IRB00277896).

**2. Objectives** (include all primary and secondary objectives)

1. Compare local wound infiltration or penile block with Exparel® plus 0.25% Bupivacaine versus 0.25% Bupivacaine alone to improve pain scores and reduce or eliminate opioid pain requirement in pediatric patients undergoing minor, outpatient urologic procedures.

2. Assess whether providing a standardized instruction guide on how to properly dispose of remaining opioid medication improves appropriate disposal (assessed as a part of QI initiative IRB00277896).

Efficacy Endpoints:

1. % of patients who are opiate-free at 48 hours and 10-14 days postop
2. Parents' postoperative pain measure (PPPM) scores at 48 hours and 10-14 days postop
3. Amount of opioid used post-discharge (oral morphine equivalents per kg)
4. Amount of opioid leftover

Safety Endpoints:

1. Incidence of pre-defined complications related to local anesthetic systemic toxicity (rare in all phase 2 and 3 trials)
2. % of families properly disposing of leftover opiate medications

Secondary Endpoint:

1. Cost comparison

**3. Background** (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

Despite increased national attention to the opioid epidemic, fatal overdose of opioids remains the leading cause of accidental death in the United States.[3] Children are not immune from this epidemic: increased opioids in the home has led to an higher incidence of accidental ingestion and intentional misuse in the young. Between 1995 and 2012, opioid-related overdoses increased by over 200% among children ages 1-4 years.[4] In adolescents (ages 15-19 years), there was a 3-fold increase in hospitalizations related to accidental poisoning by opioids, and opioid-related overdose deaths increased by 33% among adolescents and young adults ages 15-24 years from 2015-2016.[3,5]

Ambulatory surgery, which contributes to a large portion of a pediatric urologist's practice, is a leading indication for opioid prescription in children.[6] Although over 150,000 circumcisions and over 45,000 inguinal surgeries are performed on children in the United States each year, there are currently no evidence-based guidelines for if and how much opioid should be prescribed post-operatively.[7,8] As a result, the individual pediatric urologist must use his/her

own clinical judgement to decide if and how much opioid to prescribe for each individual patient, balancing the desire to ensure adequate pain management with the desire to limit excess opioid prescription. In other surgical fields, this lack of guideline has been associated with great variability between providers in opioid prescribing patterns.[9-11]

A recent study from two large academic centers demonstrated that that nearly all patients (96%) undergoing circumcision, inguinal orchiopexy, or hydrocele/hernia repair were prescribed opioid analgesia. Opioids were prescribed in higher quantities to the very young (age 0-2 years) followed by the older population (age >10 years). In addition, there was significant variability in opioid prescribing patterns between attendings and trainees, amongst individual providers, and across institutions.[1] Our finding of significant variability in opioid prescribing practices among surgeons is consistent with the existing literature.[1,10]

One study conducted at our institution confirmed trend of overprescribing of opioid medication to children undergoing pediatric urologic surgery.[2] The current practice at our institution is to provide children with 18 doses of 0.1 mg/kg/dose of oxycodone as liquid solution. The study by Hunsberger et al. found that 87% of patients used ≤18 doses, 74% used ≤12 doses, and 28% used zero opiates. Additionally, the amount of dispensed opioid remaining on completion of therapy was as follows: 95% had ≥25%, 90% had ≥50%, and 66% had >75% remaining.[2] Few patients received disposal instructions (<30%) but of those receiving disposal instructions, families were more likely to properly dispose of leftover opioid medication based on limited data (5/21 vs 2/44).[2] Thus, there is a need to evaluate mechanisms to reduce the need for opioid prescribing, as well as improve education on proper disposal of remaining opioid medication.

Exparel® is an FDA-approved non-opioid local anesthetic that is approved for single-dose infiltration to produce post-surgical local anesthesia for patients six years and older.[12] Exparel® is composed of a liposomal bupivacaine formulation that allows retention of local anesthetic at the site of injection to allow for durations as long as 72 hours.[12] Exparel® make take 3-4 hours to exert maximum analgesic effect and thus it is approved for either sequential administration or admixing with other local anesthetics such as 0.25% Marcaine. To date, no studies have evaluated the use of this local anesthetic in children undergoing urologic procedures. Exparel® may serve as a valuable tool in the pediatric urologists' pain control armamentarium to safety and effectively provide long-lasting non-opioid pain control and may allow for the reduction of elimination of opioid medications in this population.

In the present study, we will compare Exparel® plus 0.25% Bupivacaine to standard 0.25% Bupivacaine as a perioperative local analgesic. We will also simultaneously assess whether inclusion of opioid disposal instructions improved proper disposal of leftover opiate medication following the immediate postsurgical period.

## 4. Study Procedures

a. Study design, including the sequence and timing of study procedures (distinguish research procedures from those that are part of routine care).

This study will be a single-blinded prospective randomized trial in pediatric patients undergoing minor urologic surgery. Pediatric patients will be randomized in a 1:1 fashion to receive dorsal penile nerve block (circumcision, hypospadias repair, penile cyst excision, meatoplasty, chordeolysis) or spermatic cord block with local wound infiltration (orchiopexy, orchiectomy, inguinal hernia, hydrocelectomy, varicocelectomy) with Exparel® plus 0.25% Bupivacaine versus standard 0.25% Bupivacaine alone. Patient families will also be cross randomized in a 1:1 fashion to receive standard post-operative pain instructions, with or without opioid disposal instructions. Families that consent to participation in the trial will be informed of randomization to Exparel® plus 0.25% Bupivacaine versus standard 0.25% Bupivacaine but will be blinded to arm assignment. Families will also be informed that they will be receiving postoperative pain instructions, however they will not be informed of whether or not they receive opioid disposal instructions.

No other standard pre-, peri- or post-operative pediatric urologic surgery procedures will be affected. Routine care includes an initial clinic consultation, physical examination, and informed consent prior to proceeding with surgery. Informed consent for participation in the study may also be obtained in the preoperative area during the day of surgery. Eligibility will be confirmed at the time of consent. Patient will be randomized after consent is obtained and appropriate postoperative pain instructions with or without opioid disposal instructions will be given at that time to minimize drop out.

Anesthesia team will be notified when local wound infiltration or penile nerve block is being performed as is standard operating procedure, however we will not dictate what other intra or peri-operative analgesia is given. All blocks will be performed by the surgical team using landmark techniques.

Patients will be given the option of returning to the Johns Hopkins clinic or local follow-up (with a provider) for wound check approximately 7-14 days after surgery.

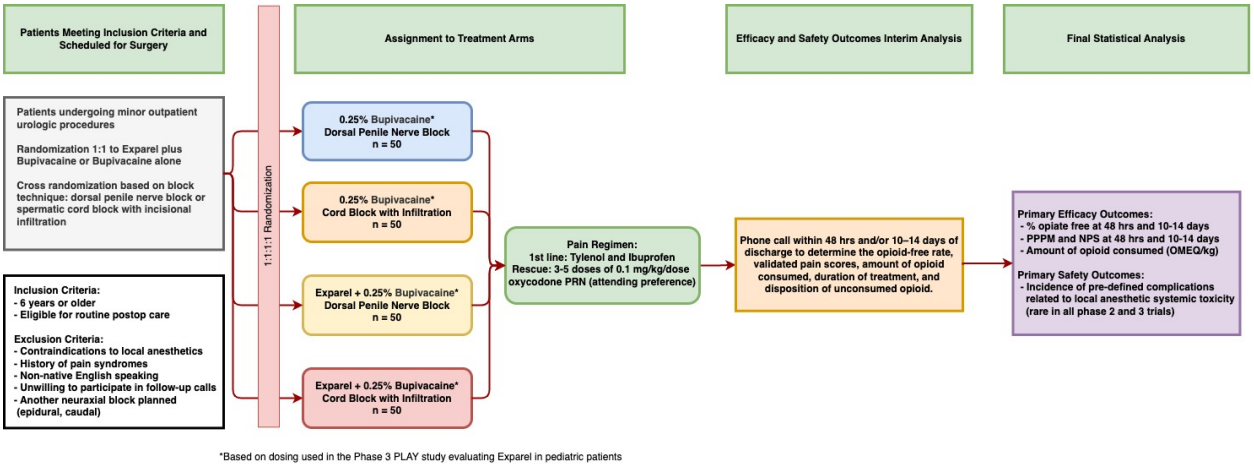


Figure 1. Diagram of plan for stratified randomization of patients to arms and outcomes assessed.

b. If your study involves data/biospecimens from participants enrolled under other research studies with a written consent or under a waiver of consent, please list the IRB application numbers for those studies. Please note: Certificate of Confidentiality (CoC) protections applied to the data in source studies funded by NIH or CDC will extend to this new study if the funding was active in 2016. If this situation applies, Section 36, question 6 in the application will need to be answered "Yes" and "Hopkins Faculty" should be selected in question 7. No other documents are required.

N/A

c. Study duration and number of study visits required of research participants.

The study protocol will be implemented during routine visits and minor pediatric urologic surgery. This includes patients undergoing orchiopexy, orchiectomy, circumcision (primary and revision), distal hypospadias repair, meatotomy/meatoplasty, chordee repair, penile cyst excision, urethrocutaneous fistula repair, inguinal hernia repair, hydrocelectomy, and varicocelectomy. Patient will receive normal postoperative follow up for a wound check and will receive phone correspondence at 48 hours and 10-14 days postoperatively to collect data regarding opioid prescribing, opioid use, pain, and disposal.

d. Blinding, including justification for blinding or not blinding the trial, if applicable.

Pediatric randomized in a 1:1 fashion to receive dorsal penile nerve block or spermatic cord block with local wound infiltration with Exparel® plus 0.25% Bupivacaine versus standard 0.25% Bupivacaine. Families will consent to enrollment in the trial to receive either Exparel® plus 0.25% Bupivacaine or standard Bupivacaine but will remain blinded to which local anesthetic is given intraoperative to ensure there is no bias between arms with respect to opioid administration or postoperative pain expectations by the family. Consent for the trial will be performed by the study coordinator and surgeons will not be aware of treatment allocation until patient is in the operating room and block is ready to be administered.

Patient families will also be cross randomized in a 1:1 fashion to receive standard post-operative pain instructions, with or without opioid disposal instructions. In order to assess the value of opioid disposal instructions, families will need to be completely blinded to this aspect of the study. Otherwise, it may bias disposal practices if we tell the family that we are assessing use of opioid disposal instructions. All families will be given standard postoperative pain instructions but will be blinded/randomized to receive opioid disposal instructions or not.

e. Justification of why participants will not receive routine care or will have current therapy stopped.

All patients will receive routine care. Both arms include patients receiving accepted standards of care.

f. Justification for inclusion of a placebo or non-treatment group.

Not applicable, no placebo or non-treatment arm was included in the study. Both arms will receive FDA-approved local analgesics.

g. Definition of treatment failure or participant removal criteria.

Not applicable. Patients will have rescue opioid medication if the treatment arm does not provide adequate pain relief perioperatively.

h. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

Given that the interventions will only take place in the perioperative period, no additional measures would need to be taken if the study were to be terminated prematurely. Further enrollment would stop and all patients would resume standard of care of local wound infiltration or penile nerve block with standard 0.25% Bupivacaine.

i. If biological materials are involved, please describe all the experimental procedures and analyses in which they will be used.

N/A

## 5. Inclusion/Exclusion Criteria

**Inclusion:**

1. Pediatric patients 6 years of age and older undergoing minor urologic surgery
2. Patients who are otherwise eligible to receive routine care following minor urologic surgery

**Exclusion:**

1. Contraindication to receiving local anesthetics (i.e. pre-existing cardiac, renal, hepatic dysfunction)
2. Pediatric patients younger than 6 years of age
3. Pediatric patients with a history of pain syndromes or are unable to tolerate opiate medication
4. Unwilling or unable to participate in 48 hours and 10-14 day follow-up phone calls

## 6. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.

Exparel® is composed of a liposomal bupivacaine formulation that allows retention of local anesthetic at the site of injection to allow for durations as long as 72 hours.[12] To date, no other long lasting non-opioid pain control exists for pediatric patients undergoing surgery.

Per the Exparel® dosing and administration guide, the maximum recommended dose for Exparel® is 4 mg/kg. Bupivacaine may be given concurrently with Exparel as long as the ratio of the milligram dose of bupivacaine HCl to Exparel does not exceed 1:2 (50% of the mg dose of Exparel).[12] Each Exparel® contains 133 mg of liposomal bupivacaine in 10 ml saline, or 13.3 mg/ml. 0.25% bupivacaine contains 2.5 mg/ml of bupivacaine. Patients randomized to the intervention arm received sequential weight-based administration of 0.5 mg/kg (maximum recommended dose 2.5 mg/kg) of 0.25% bupivacaine hydrochloride without epinephrine followed by 2.5 mg/kg (maximum recommended dose 4 mg/kg) of 1.33% liposomal bupivacaine such that the ratio of the milligram dose of bupivacaine hydrochloride to liposomal bupivacaine did not exceed 1:2 (50% of the mg dose of liposomal bupivacaine) as described in the medication dosing insert.

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.

Exparel® is an FDA-approved non-opioid local anesthetic that is approved for single-dose infiltration to produce post-surgical local anesthesia for pediatric patients six years and older.[12]

c. Justification and safety information if non-FDA approved drugs without an IND will be administered.

N/A

**7. Study Statistics**

a. Primary outcome variable.

The primary efficacy endpoints will be the percentage of pediatric patients who are opiate-free at 48 hours and at 10-14 days postoperatively, parents' postoperative pain measure (PPPM) scores at 48 hours and 10-14 days postoperatively, amount of opioid used following discharge (as measured by weight based oral morphine equivalents), and the amount of opioid leftover at 10-14 days.

The primary safety endpoints will be the incidence of pre-defined complications related to local anesthetic systemic toxicity (exceedingly rare in all phase 2 and 3 trials), and the percentage of families properly disposing of leftover opiate medication at 10-14 days postoperatively.

The primary analysis will involve two separate comparisons: 1) Comparison of primary efficacy endpoints between those receiving Exparel® plus 0.25% Bupivacaine versus those receiving standard 0.25% Bupivacaine alone, and 2) Comparison of primary safety endpoints between those receiving Exparel® plus 0.25% Bupivacaine versus those receiving standard 0.25% Bupivacaine alone.

b. Secondary outcome variables.

Secondary outcomes will include a cost comparison of Exparel® plus 0.25% Bupivacaine versus standard 0.25% Bupivacaine alone, as well as evaluating efficacy of using Exparel® for a penile nerve block versus incisional infiltration with regard to safety and efficacy.

c. Statistical plan including sample size justification and interim data analysis.

All patients that meet inclusion criteria for the trial and are consented will undergo cross-randomization (Figure 1) to receive either 0.25% Bupivacaine or Exparel® plus 0.25% Bupivacaine, opioid medication instructions with disposal instructions, or opioid medication instructions without disposal instructions.

Currently at Johns Hopkins, we perform over 500 minor pediatric urologic procedures per year, roughly 20% of which involve patients 6 years or older and could be eligible for inclusion.

We assumed that the smallest detectable difference in the primary endpoints may be the percentage of patients who are opiate-free at 48 hours and thus planned to base our power calculation on detecting a difference in this variable. Prior studies from our institution have demonstrated that roughly 28% of pediatric patients undergoing minor urologic procedures and receiving standard Bupivacaine local wound infiltration require zero opioids postoperatively.[2] This study will be conducted with a superiority design (does penile block or wound infiltration with Exparel® plus 0.25% Bupivacaine offer a superior opiate-free rate at 48 hours than standard Bupivacaine?).

Power of 80% (beta = 0.2) and two-sided alpha of 0.05 for increasing opiate-free rate

28% to 60%: n = 74; 37 in each arm
28% to 50%: n = 152; 76 in each arm
28% to 40%: n = 486; 243 in each arm
28% of peds uro pts from recent JHH anesthesia study required zero opiates

Consensus among the study investigators suggested that a 50% opioid-free rate at 48 hours (22% absolute difference between arms) would be the minimal clinically relevant difference in the primary outcome measure.

Assuming a 25% rate of lost-to-follow-up or incomplete follow-up data, we will plan to enroll 100 pediatric patients per arm, or 200 patients total. Target enrollment may be subject to change if the lost to follow-up rate is significantly higher or lower than 25%.

Randomization lists will be generated by the study coordinator. The investigators will maintain the randomization list, password protected, on a remote drive maintained by the Department of Urology and will provide the random assignment to the study coordinator as each patient is enrolled.

One interim analysis of the primary efficacy and primary safety endpoint will be planned with potential early stopping for efficacy or futility. The interim analysis will be conducted after half

of the patients have been enrolled. O'Brien-Fleming boundaries will be used, as implemented in PASS v. 11 (NCSS Software, Inc., Kaysville, UT).

One interim analysis of the primary efficacy endpoint will be conducted after information proportion of 0.66 (n = 102) to assess for early stopping for efficacy or futility. The total sample size needed for 80% power with a 1-sided test was 152 patients (76 per arm), based on 10,000 simulations. Alpha-spending at the interim analysis and final analysis was 0.016 and 0.034 (cumulative alpha spent 0.016, 0.05), respectively. The futility boundaries at the interim analysis and final analysis were p=0.24 and p=0.048, respectively. At the interim analysis the rates of all-cause surgical complications and those attributable to sequela of the local anesthetics or symptoms related to LAST were also evaluated. An unacceptable rate of all-cause surgical complications was >10%. If the lower 95% confidence bounds met or exceeded this rate for all-cause complications or there were any episodes of LAST, the trial would have been halted for further review and consideration of early stopping.

*Statistical Analysis*

For each arm of the cross-randomization, groups will be compared to identify any imbalance after randomization in relevant characteristics. Comparisons will include factors such as age, race, BMI, comorbidities, surgery type, operative time. Discrete factors will be compared with chi-squared test, and continuous factors will be compared with Mann Whitney U test given prior data suggesting these data will not follow a normal distribution. If data do conform to a normal distribution will utilize t test.

Analysis of the primary efficacy outcome will compare rate of opioid-free rate at 48 hours postoperatively between patients receiving Exparel® plus 0.25% Bupivacaine versus standard 0.25% Bupivacaine alone, using chi-squared test. Logistic regression will be used if adjustment is required for any potential confounders not balanced by randomization, with the treatment effect estimated by the odds ratio and 95% confidence interval. Similar comparison of univariate rates, and adjusted odds ratios will be used for the primary safety endpoints.

All analyses of primary and secondary outcomes will be based on intention to treat (ITT). Per protocol analyses will also be conducted, but treatment success will be based on ITT.

d. Early stopping rules.

The present trial will be stopped prematurely if ANY of the following events occur:
- The trial satisfies futility at interim analysis
- There is a change in the FDA approval status of Exparel®

**8. Risks**

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

Administration of Exparel®/Standard Bupivacaine

1. Major risks:

a. CNS toxicity (very rare, ie. tinnitus, confusion)
b. Cardiovascular toxicity (very rare, ie. bradycardia, AV block)

2. Minor risks:
    a. Gastrointestinal discomfort (less than 1% of patients reported in PLAY phase III trial)
    b. Shortness of breath (less than 1% of patients reported in PLAY phase III trial)
    c. Constipation (roughly 10% reported in PLAY phase III trial)
    d. Bruising at injection site (common but short-lived and similar to that of other standard local anesthetics)

b. Steps taken to minimize the risks.

Local anesthetics are frequently administered by the operating surgeon at the time of minor urologic procedures in pediatric patients. All local anesthetics administered in this study will be done intraoperatively while the patient is being monitored with non-invasive blood pressure and peripheral oxygen saturation measurements. Avoidance of intravascular injection of all local anesthetics will be performed via visual inspection on aspiration prior to injection. Additionally, the surgical team will ensure the administered local anesthetic dose does not exceed the maximal recommended dose (2 mg/kg for Bupivacaine or 4 mg/kg for Exparel). All patients will also be observed in the recovery area postoperatively for at least one hour to ensure none of the aforementioned side effects occur, in accordance with standard practice at Johns Hopkins.

c. Plan for reporting unanticipated problems or study deviations.

Unanticipated problems or concerns will be reported by the in-hospital urology team to the research coordinator(s) of the trial as well as the principal investigator. A plan of action will be developed and implemented with open communication with the IRB and appropriate avenues for reporting adverse events. The Hopkins Event Reporting Online (HERO) system can also be utilized as needed.

d. Legal risks such as the risks that would be associated with breach of confidentiality.

There are no anticipated legal risks with breach of confidentiality specifically associated with the trial. Those participating in the trial will receive the usual care afforded to all pediatric patients undergoing minor urologic procedures.

e. Financial risks to the participants.

Both arms of the trial consist of accepted practice standards. Patients and their respective insurance will be responsible for the cost of routine care including surgery and postoperative follow-up which will be unaffected by the study.

## 9. Benefits

a. Description of the probable benefits for the participant and for society.

Patients participating in the trial receiving Exparel®, which can be considered an acceptable standard of care, may experience reduced pain in the immediate postoperative period following minor urologic procedures as well as be spared of the need for opioid medication. Patient receiving 0.25% Bupivacaine, which is also considered an acceptable standard of care, will experience no benefits beyond receiving the routine perioperative care for patients undergoing minor pediatric urologic procedures.

Patients randomized to receive opioid disposal instructions may benefit by reducing leftover opiate medication in the household, which may subsequently reduce the risk of accidental ingestion or overdose.

The potential benefit for society would be the ability to assess whether Exparel® plus 0.25% Bupivacaine is superior to 0.25% Bupivacaine alone to improve pain scores and reduce need to prescribe opioid medication for minor pediatric urologic surgery.

**10. Payment and Remuneration**

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

Patients will receive no compensation or penalties associated with completing or not completing the protocol.

**11. Costs**

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

The administration of 0.25% Bupivacaine in the perioperative setting is an established method of local analgesia and will be included in the routine costs of surgical and outpatient care. The cost to participants will be negligible, estimated at $5 per dose. These costs are generally covered by medical insurance.

Exparel® obtained as part of the study will be covered by the study and will not be transferred to the patient.

**12. Transfer of Materials**

Transfer of biospecimens from Johns Hopkins to another organization for research purposes and receipt of biospecimens from an outside organization for your research must adhere to JHU policies for material transfer and biospecimen transfer.

N/A

## 13. References:

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