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Perioperative Tissue Penetration of Antimicrobials in Infants

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Phase 1/2 Trial

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Statement of Compliance

This trial will be conducted in compliance with the protocol, International Conference on Harmonization (ICH) guideline E6: Good Clinical Practice (GCP): Consolidated Guideline, and the applicable regulatory requirements from the United States Code of Federal Regulations (CFR), including but not limited to 45 CFR 46 (human participants protection, incorporating Subpart D Additional Protections for Children involved as Subjects in Research), 21 CFR part 50 (informed consent, incorporating Subpart D Additional Safeguards for Children in Clinical Investigations), and 21 CFR part 56 (institutional review board [IRB]).

All individuals responsible for the design and/or conduct of this study have completed Human Participants Protection Training and are qualified to be conducting this research.

PI	Principle investigator
cIAI	Complicated intraabdominal infection
CI	Confidence interval
Cr	Serum creatinine
CRF	Case report form
DCRI	Duke Clinical Research Institute
EKG	Electrocardiogram
GCP	Good clinical practice
GI	Gastrointestinal
ICF	Informed consent form
IEC	Institutional ethics committee
IRB	Institutional review board
ITT	Intent to treat
IV	Intravenous
PK	Pharmacokinetic
PD	Pharmacodynamic
REB	Research ethics board
SAP	Statistical analysis plan
SAE	Serious adverse event
SoA	Schedule of activities
WBC	White blood cell count
Hg	Hemoglobin
HCT	Hematocrit
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ESR	Erythrocyte sedimentation rate
CRP	C-Reactive Protein
PK	Pharmacokinetics
PD	Pharmacodynamics

Protocol Synopsis

Protocol Title:	Perioperative Tissue Penetration of Antimicrobials in Infants
Phase:	1/2
Product:	Metronidazole
Objectives:	Primary: 1) Characterize the PK of metronidazole and its metabolite 2-hydroxymetronidazole in the plasma and intestinal wall of healthy infants undergoing intestinal surgeries Secondary: 1) Characterize the contribution of intestinal CYP2A6 metabolism on metronidazole
Study Design:	Prospective, single center, open-label, PK study
Study Population:	Children $\leq$ 2 years of age undergoing intestinal surgery
Number of Participants:	Up to 20
Number of Sites:	1
Duration of Participant Participation:	Day of surgery. Remote monitoring of patient record for 30 days postoperatively
Dose Schedule:	Per routine medical care
Estimated Start:	May 2020
Estimated Time to Complete Enrollment:	18 months
Inclusion Criteria	1) Age 0 to $\leq$ 2 years at enrollment 2) Written informed consent provided by a parent or legal guardian 3) Scheduled to undergo elective intestinal operation for the removal of non-infected bowel 4) Sufficient intravascular access to complete the study procedures
Exclusion Criteria:	1) Prior treatment with metronidazole for any dose during the 72 hours prior to study drug administration. 2) Patients with active inflammatory or infectious conditions of the bowel such as inflammatory bowel disease, Hirschprung's disease in the portion of bowel to be excised, diverticular disease, cancerous or pre-cancerous lesions, colitis, enteritis, ulcerative disease, Meckel's diverticulum, celiac disease, and irritable bowel syndrome. 3) Renal dysfunction defined as serum creatinine >2 mg/dL at enrollment

	4) Receiving any extracorporeal life support including extracorporeal membrane oxygenation, ventricular assist devices, and renal replacement therapy at enrollment 5) Any condition or circumstance that, in the opinion of the investigator, would compromise the safety of the participant or the quality of the data.

Table 1. Schedule of Study Procedures

Assessments	Screening Period	Treatment Period	Postoperative Period
	Day -30 to 0	Operative Day, Day 1	Day 2 to Day 31
Informed consent/assent	X		
Demographics[a]	X		
Clinical data[b]			
Medical history	X		
Physical examination	X	X	
Height/length and body weight	X	X	
Vital signs[c]	X	X	
Clinical laboratory parameters[d]	X	X	
Serum creatinine	X	X	
Study drug administration		X	
Events of Special Interest[e]		X	X
Adverse Events[f]	X	X	X
Intraoperative Complications[g]		X	
Postoperative Complications[g]		X	X
Prior and Concomitant therapy	X	X	
Pharmacokinetic data			
PK sample collection			
Plasma sample collection		X	
Intestine sample collection		X	

a: Demographics to be included: gender, date of birth, age, race, comorbidities, gestational age at birth and birth weight
b: May be obtained through review of electronic medical record. All assessment or laboratory collections performed as standard of care only. No assessments or blood draws other than PK data are performed solely for the purposes of this study
c: Vital signs to be included: weight, height, heart rate, respiratory rate, oxygen saturation, and blood pressure
d: Clinical laboratory parameters to be included: WBC, Hg, HCT, Plt, PT, PTT, BUN, serum creatinine, potassium, sodium, AST, ALT, total bilirubin, albumin, prealbumin, ESR, CRP, any blood, tissue, urine cultures as obtained per standard of care
e: Events of Special Interest include: gastrointestinal surgeries, sepsis, wound infection, urinary tract infection, feeding intolerance, transfusion requirements, phlebotomy complications
f: Adverse events related to study procedures (ie phlebotomy)
g: Complications will be assessed through the electronic medical record including excessive blood loss, transfusion requirements, injury to any organ system, infection in any organ system including wound bed, unanticipated return to the operating room, and any unexpected intra- or postoperative occurrence that requires medical or surgical attention

1 KEY ROLES

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2 BACKGROUND INFORMATION AND RATIONALE

2.1 Background Information

2.1.1 Complicated Intra-Abdominal Infections

Complicated intra-abdominal infections (cIAI) are a leading of cause of infant morbidity and mortality. Up to 14% of high-risk infants develop cIAI[1], and up to 30% of those affected die[2]. Common infantile cIAIs involve bowel necrosis or perforation from necrotizing enterocolitis, Hirschsprung disease, gastroschisis, or omphalocele. Bacterial translocation from intestinal lumen into the intestinal wall is a key pathophysiologic component of cIAI[3].

2.1.2 Current Antibiotic Practice

Current antibiotic regimens for cIAI are derived to achieve bactericidal plasma concentrations, but whether these dosing regimens result in appropriate antibiotic concentrations in the intestinal wall of infants is unknown[4-6]. cIAI treatment regimens vary, but multi-agent therapy and coverage against anaerobes including *Bacteroides* and *Clostridium* species is recommended and commonly achieved in infants with metronidazole[7].

2.1.3 Antibiotic Penetration of the Intestine

Intestinal wall concentrations of antibiotics are essential to treat local bacterial infection and improve outcomes. Failure to reach optimal antibiotic concentrations in the intestinal wall may result in abscess formation, intestinal necrosis, and secondary bacteremia, thus worsening clinical outcomes[3]. Optimizing intestinal wall concentrations of antibiotics in infants with cIAI is therefore an urgent and unmet public health need. Antibiotic uptake from the blood stream into the intestinal wall and local metabolism determine tissue concentrations, and are complex and understudied processes dependent on perfusion, endothelial integrity, and expression and function of transporters and metabolizing enzymes[8]. These processes are affected by both pathophysiologic alterations of cIAI and by infant growth and maturation[9]. Prior studies attempting to understand this relationship sampled enteric flora or peritoneal fluid, but none directly studied human intestinal tissue[10]. These alternate approaches precluded characterization of both intestinal wall absorption and intestinal wall metabolism of metronidazole, the latter occurring primarily via cytochrome P450 (CYP) 2A6.

2.1.4 Metronidazole Metabolism

The primary metabolizing enzyme of metronidazole is CYP2A6 and metronidazole's primary metabolite is 2-hydroxymetronidazole, which can exhibit up to 65% of metronidazole's antimicrobial activity. CYP2A6 exhibits significant ontogeny in liver and oral mucosal tissues, and adult intestinal wall expression is highly variable (CV%>50%). However, ontogeny and interindividual variability of CYP2A6 expression and activity in the intestinal wall of infants are unknown[11,12].

2.2 Study Rationale

Our overarching hypothesis is that intestinal wall penetration of metronidazole in infants will vary with age and require optimization of current dosing regimens designed to target plasma exposure only. To test this hypothesis, we will perform an opportunistic PK study of infants receiving perioperative

metronidazole per standard of care at the time of scheduled intestinal resection surgery. Plasma and intestinal wall samples will be collected intra-operatively following administration of metronidazole for measurement of metronidazole and its primary metabolite concentrations in the plasma and the intestinal wall. These data will be used to characterize the pharmacokinetics of metronidazole in plasma and intestinal wall of infants.

2.3 Potential Risks and Benefits

2.3.1 Risk Assessment

Risks of Intestinal Sampling

There are risks to removing the intestine of a patient, however patients enrolled in this study are already undergoing bowel excision for clinical indications described in section 5 in the study design section. A small piece (goal 500mg) of bowel will be taken from the excised portion of bowel, but no additional bowel will be excised for the purpose of this study. Therefore, no additional risk of surgery will be introduced through participation in this study. There will be no discomfort associated with intestinal excision as the patient will be under general anesthesia as per standard of care.

Risks of Blood Drawing

There are risks to blood sampling, usually some pain/discomfort with the blood draw/stick however the patient will be under anesthesia during the time of IV insertion per standard of care for surgery. Every effort will be made to use an already established intravenous line, rather than a new access site. Less than 5mL of blood will be sampled in total, therefore this will not contribute to a clinically significant amount of blood loss.

Risk of Loss of Confidentiality

There is a potential risk of loss of confidentiality. Every effort will be made to protect participants' confidential information, but this cannot be guaranteed. All patients will be assigned a study number and de-identified information will be housed on a Duke RedCAP database with access only granted to study personnel who have had the appropriate training regarding HIPPA compliance and confidentiality.

Unforeseen Risks

There may be other risks to the participant from this research that are not known or foreseeable at this time.

2.3.2 Benefit Assessment

This study will provide pediatric population-specific safety, PK, and preliminary efficacy data for metronidazole administered per standard-of-care in children with cIAI.

2.3.3 Overall Benefit: Risk Conclusion

Considering the measures taken to minimize risk to participants in this study, the potential risks identified are justified by the anticipated benefits that may be afforded to patients with cIAI.

3 OBJECTIVES

Table 1 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
Characterize the PK of metronidazole and its metabolite 2-hydroxymetronidazole in the plasma and intestinal wall of healthy infants undergoing intestinal surgeries	Primary and secondary PK parameters including clearance, half-life, volume of distribution, and AUC
Secondary	
Characterize the contribution of intestinal CYP2A6 to the metabolism of metronidazole	CYP2A6 quantification, ratios of metronidazole to 2-hydroxymetronidazole concentrations, ratios of metronidazole in plasma/intestine, ratios of 2-hydroxymetronidazole concentration in plasma/intestine

3.1 Study Outcome Measures

3.1.1 Primary Outcome Measures

1) PK parameters after administration of metronidazole and its metabolite 2-hydroxymetronidazole in the plasma and intestinal wall which may include:
   - Clearance (CL)
   - Half-life (t1/2)
   - Volume of distribution (V)
   - Area under the curve (AUC)

3.1.2 Secondary Outcome Measures

1) CYP2A6 quantification and other metabolizing and transporter enzymes
2) Ratios of metronidazole to 2-hydroxymetronidazole concentrations
3) Ratios of metronidazole in plasma/intestine
4) Ratios of 2-hydroxymetronidazole concentration in plasma/intestine

4 Study Design

Single center, open-label, non-randomized study to assess the intestinal pharmacokinetic profile of metronidazole in healthy children ≤ 2 years of age undergoing elective intestinal operations for non-infectious conditions.

4.1 Number of Desired Participants:

A 20 infant sample size is derived to meet the primary objective of characterizing the PK of metronidazole in plasma and the intestinal wall of infants. Two desired gestational age ranges will be included in this study:

- < 34 weeks gestational age
- ≥ 34 weeks gestational age

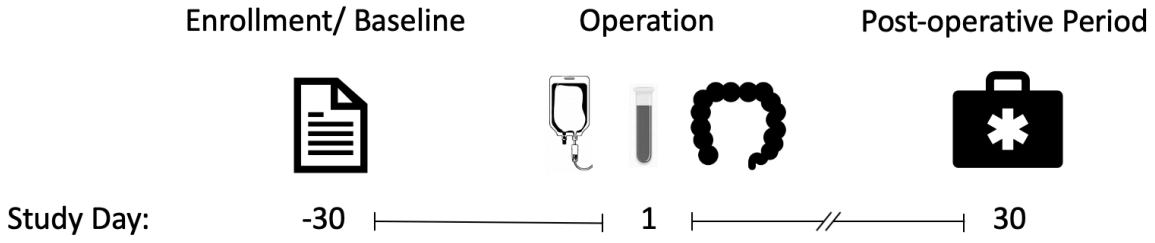
All efforts will be made to approximately stratify enrollment as outlined in table 2.

Table 2 Age Stratification

Age	N = 20
< 34 weeks gestational age at birth	10
≥34 weeks gestational age at birth	10

Note: "Enrolled" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study after completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

4.2 Study Schema



5 Study Population

5.1 Inclusion Criteria

1. Age 0 to ≤ 2 years
2. Written informed consent provided by a parent or legal guardian
3. Scheduled to undergo elective intestinal operation for the removal of non-infected, otherwise healthy bowel
4. Sufficient intravascular access to complete the study procedures

5.2 Exclusion Criteria

1) Prior treatment with metronidazole for any dose during the 72 hours prior to study drug administration.
2) Patients with active inflammatory or infectious conditions of the bowel such as inflammatory bowel disease, Hirschprung's disease in the portion of bowel to be excised, diverticular disease, cancerous or pre-cancerous lesions, colitis, enteritis, ulcerative disease, Meckel's diverticulum, celiac disease, and irritable bowel syndrome.
3) Renal dysfunction defined as serum creatinine >2 mg/d at any time during the preoperative period.
4) Receiving any extracorporeal life support including extracorporeal membrane oxygenation, ventricular assist devices, and renal replacement therapy.
5) Any condition or circumstance that, in the opinion of the investigator, would compromise the safety of the participant or the quality of the data.

5.3 Duration of Study Participation

The maximum duration of participation is approximately 60 days: Screening Period of approximately 30 days, a 1-day Treatment Period on the day of the operation, and a 30-day Follow-Up Period.

5.3.1 Replacement Participants

Because accurate characterization of PK in a small sample size of patients is dependent upon adequate sampling, participants in this study who are unable to provide at least 1 timed PK sample may be replaced. The replaced patient will be considered an early withdrawal from the study and will be monitored for AEs related to study procedures, complications, and events of special interest as per protocol. The data collected from the replaced patient will be retained and included in the study results.

5.3.2 Reasons for Participant Withdrawal

A participant's parent/guardian may voluntarily discontinue their child's participation in this study at any time. The investigator may also, at his/her discretion; withdraw the participant from this study at any time. Participants may be prematurely discontinued from the study for any of the following reasons:

- Participant or investigator noncompliance with the study protocol
- At the request of the participant's parent/guardian, investigator, or sponsor
- Safety concerns

Participants are not obligated to state the reason for withdrawal. The reasons for withdrawal, or failure to provide a reason, must be documented by the investigator on the completion/ withdrawal section of the CRF. Any participant who withdraws early or is withdrawn early will be requested to complete end-of-study safety evaluations and will be provided appropriate care under medical supervision until the symptoms of any events of special interest resolve or the participant's condition becomes stable. Participants withdrawn from the study due to an event of special interest must be followed per protocol (See Section 8)

5.3.3 Termination of Study

The study will be terminated upon study completion. The study is considered closed when all required documents and study supplies have been collected and a study-site closure meeting has occurred. The Investigator may initiate study closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.
Reasons for the early termination of the study may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the investigators will notify, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participants and should assure appropriate therapy and/or follow-up as necessary.

6 STUDY PROCEDURES

6.1 Screening

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed unless approved by the study PI and IRB. Immediate safety concerns should be discussed with the PI immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log of consented patients to record details of all participants screened and to confirm eligibility or record reasons for screen failure, as applicable. Procedures conducted as part of the participant's routine preoperative management (eg, blood count, creatinine) and obtained before signing of the ICF may be used for screening or baseline purposes provided the procedures meet the protocol-specified criteria and are performed within the time frame defined in the SoA. If a patient does not have desired laboratory values, they will be obtained through standard of care measurements as able, most often occurring during preoperative visits to either surgery or anesthesia, in hospital consultations to surgery, or in the standard of care preoperative laboratory collection on the day of surgery.

This study will consist of a Screening, Treatment, and Postoperative Period.

6.2 Enrollment/Baseline

Screening Period (Day -30 to 0)
After the parent or legal guardian has signed the IRB-approved informed consent form/HIPAA authorization documents, and after it has been determined that the participant satisfies all inclusion and no exclusion criteria, the following evaluations will be extracted from the electronic medical record:

1) Participant demographics including gender, date of birth, postnatal age, race, gestational age at birth and birth weight
2) Physical examination and vital signs, including weight, height, heart rate, respiratory rate, oxygen saturation, and blood pressure, performed at any preoperative visit
3) Pertinent medical history, including diagnosis for which subject is undergoing surgery and history of genetic syndrome (i.e., trisomy 21)
4) The most recent laboratory determination in pre-operative visits, including serum creatinine, no blood draws will be performed just for the purposes of this study (See Section 6.6)
5) Adverse events related to study procedures

6.3 Treatment Procedures

Operative Day (Day 1)

The following assessments will be conducted on the day the patient is administered the study drug and undergoes surgery.

1) Date, time, dose, route, and duration of metronidazole administration
2) Physical examination and vital signs, including weight, height, heart rate, respiratory rate, oxygen saturation and blood pressure, can be performed prior to intubation on the day of surgery
3) Laboratory determinations, if available, no blood draws will be performed just for the purposes of this study (See Section 6.6)
4) Concomitant medications of interest
5) Collection of PK plasma and intestine samples (including date/time; See Section 6.6.2)
6) Results for laboratory tests of interests (See Section 6.6.1)
7) Events of special interest (See Section 8.1)
8) Adverse events related to study procedures (See Section 8.4)
9) Information regarding the surgery performed including: type of surgery, laparoscopic vs. open procedure; times of incision, intestinal excision, closure; intubation, extubation; estimated blood loss, blood transfusions given, amount and type of intravenous fluids given
10) Intraoperative complications including: unexpected alteration in operative plan, excessive blood loss, need for transfusion, damage to any structure, conversion from laparoscopic to open procedure, death (See Section 8.2)

6.4 Postoperative Period

The postoperative period of 30 days will be followed remotely through review of the electronic medical record. If no clinical contact has been made by the end of the postoperative period, study personnel will phone the parent/guardian to examine for any adverse events or hospitalizations to the participant.

1) Information regarding any adverse events related to metronidazole administration and/or study procedures (see section 8.4)
2) Information regarding events of special interest (See Section 8.1)
3) Information regarding postoperative complications including: any unexpected medical or surgical intervention, readmission for any reason, postoperative blood loss, transfusion requirements, infectious complications of any organ system or the wound, death (See section 8.3)

6.5 End of Therapy OR Early Withdrawal/Discontinuation

As the active participation in the study is only on the day of surgery, it is unlikely that many participants would receive the study drug and not have any samples taken as that time period is usually less than a few hours. Postoperative monitoring will be done remotely, however if any parent/ guardian wishes to be removed from the study and their child's data no longer monitored through the electronic health record, data collection will stop on that patient.

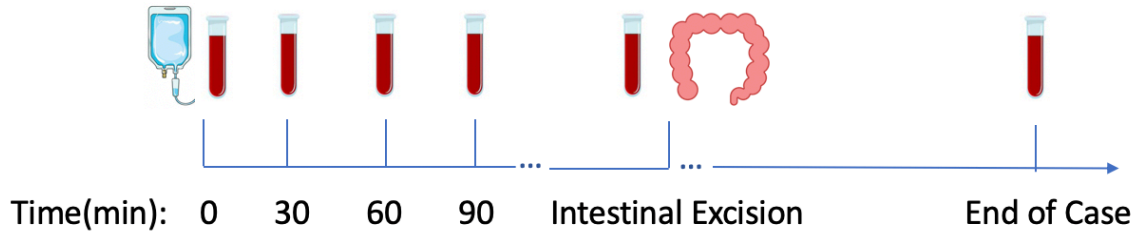
6.6 Laboratory Evaluations

6.6.1 Clinical Laboratory Evaluations

For all time points, the following labs may be recorded while the patient is on study if collected per standard of care.

1. Any serum chemistry values obtained during perioperative visits prior to or on the day of surgery and during duration any postoperative stay. These include: WBC, Hg, HCT, Plt, PT, PTT, BUN, serum creatinine, potassium, sodium, AST, ALT, total bilirubin, albumin, prealbumin, ESR, CRP. If multiple values for a laboratory are obtained in the pre- or post-operative period, the values recorded will be the value closest to the day of surgery.

6.6.2 Special Assays or Procedures



Intraoperative plasma samples will be obtained from pre-existing vascular access catheters at end of bolus, 30, 60, 90 minutes, at time of intestinal excision(s), and at the end of the case in ethylenediaminetetraacetic acid microcontainers, exceeding no more than approximately 5 mL total (Figure 2). Additional plasma can be collected if the child remains in the hospital either in the recovery room or on the surgical ward at times 3-4 hours, 4-6 hours, and 6-12 hours from infusion of metronidazole, however these samples are not necessary for a participant to be included in the study analysis. At the time of intestinal excision, the surgeon will cut at least 500 mg of intestine from the specimen, ensuring all layers of bowel are included. If more than one intestinal sample is taken during the surgery, such as in the case of multiple strictures removed, each sample will be obtained and labeled appropriately. The sample(s) will be placed in a sterile, dry container.

All samples will be frozen in liquid nitrogen and stored in a -80°C freezer within 1 hour of acquisition. Samples will be batched and shipped to a central laboratory for concentration measurement of metronidazole and its primary metabolite 2-hydroxymetronidazole using a HPLC/MS/MS plasma assay previously developed and validated per FDA guidance[13]. The plasma and intestine samples will also be assayed for CYP2A6, transporters, and metabolizing enzymes though protein quantification assays at a proteomics laboratory.

Every effort should be made to collect all PK samples, and the timing of PK sampling with standard-of-care blood draws when possible. Collection of PK samples outside the windows provided in the sampling will not be considered protocol deviations.

If a procedure is shorter than the 90 minutes, this PK sample will not be taken. Similarly, if the procedure is less than an hour the 60- and 90-minute samples will not be obtained. Finally, in the unlikely event that

a procedure is less than 30 minutes, only the end of bolus, intestinal excision, and end of case samples will be taken.

6.6.3 Example PK Sample Schedule

Sample Number	Time after end infusion of metronidazole (min)*	Type of Sample
#1	0 – At end infusion	Plasma
#2	30	Plasma
#3	60	Plasma
#4	90	Plasma
#5	Time of intestinal excision	Plasma
#6	Time of intestinal excision	Intestine
#7	Time of skin closure	Plasma

*Plasma samples will be accepted +/- 10 minutes from ideal blood draw time

6.7 Concomitant medications

The name, daily dose, and date of administration of each concomitant medication of interest will be recorded for all doses given from day of surgery until the end of the study. Medications of interest include:

- Other systemic antimicrobials
- Oral anticoagulants
- Inducers of CYP 2A6:
  - Rifampicin
  - Barbiturates such as amobarbital, pentobarbital, phenobarbital and secobarbital
- Inhibitors of CYP 2A6 such as:
  - Amiodarone
  - Amlodipine
  - Buprenorphine
  - Clofibrate
  - Clotrimazole
  - Desipramine
  - Disulfiram
  - Entacapone
  - Fenofibrate
  - Gabapentin,
  - Isoniazid
  - Ketoconazole
  - Letrozole
  - Methimazole
  - Methoxsalen

- Metyrapone
- Miconazole
- Modafinil
- Orphenadrine
- Pilocarpine
- Selegiline
- Sulconazole
- Tioconazole
- Tranylcypromine

7 STUDY PRODUCT DESCRIPTION

7.1 Dosage and Study Drug Information

7.1.1 Rationale for Dose Selection

Dosing will not be prescribed by this protocol. Dosing will be per standard of care and at the discretion of the treating physician.

7.1.2 Dose Frequency

Frequency of metronidazole dosing will be at the discretion of the treating physician.

7.1.3 Study Drug

This protocol does not specify the brand of product nor dosing amount or interval. Product will be "off the shelf" metronidazole as determined by the site.

7.1.4 Preparation and Administration of Study Intervention/ Investigational Product

The local pharmacy will prepare the metronidazole per standard of care.

8 ASSESSMENT OF SAFETY

8.1 Events of Special Interest

Events of special interest to be collected include:

1. Gastrointestinal surgeries subsequent to index surgery
2. Intestinal strictures as defined by the primary clinical team
3. Sepsis as defined by the clinical team or positive blood cultures with an organism not typically considered a contaminant
4. Wound infection as defined by clinical team or positive wound cultures with an organism not typically considered a contaminant
5. Urinary tract infection defined as a positive urine culture with an organism not typically considered a contaminant
6. Feeding intolerance as defined by the clinical team or the insertion of any type of decompression or feeding tube
7. Transfusion requirements with any blood product
8. Phlebotomy related issues such as thrombophlebitis, hemorrhage, and thrombus

8.2 Intraoperative Complications

An intraoperative complication will be limited to any issue arising from the time the patient enters the operating room until the time that the patient leaves the operating room. Intraoperative complications are defined as instances where the anesthesia or surgical team alter treatment or surgical management to address an issue. All intraoperative complications documented by the anesthesia or surgical teams in the electronic medical record will be collected and their severity classified using the CLASSIC scale below[14].

CLASSIC Grade	Definition
Grade 0	No deviation from the ideal intraoperative course
Grade 1	Any deviation from the ideal intraoperative course without the need of any additional treatment or intervention
Grade 2	Any deviation from the ideal intraoperative course with the need of any additional treatment or intervention not life-threatening and not leading to permanent disability
Grade 3	Any deviation from the ideal intraoperative course with the need of any additional treatment or intervention life-threatening and/or leading to permanent disability
Grade 4	Any deviation from the ideal intraoperative course with death of the patient

8.3 Postoperative Complications

A postoperative complication will be limited to any issue arising after the patient leaves the operating room to 30 days after the operation. Postoperative complications are defined as any issue arising that

leads to alteration in the standard recovery pathway. All postoperative complications documented by the anesthesia or surgical teams in the electronic medical record will be collected and their severity will be classified using the Clavien-Dindo scale below[15].

Clavien-Dindo Grade	Definition
Grade 0	Standard postoperative care without deviations from protocols
Grade 1	Any deviation from postoperative care without the need for pharmacologic, surgical, radiologic, or endoscopic interventions. (Allowed interventions – antiemetics, antipyretics, analgesics, diuretics, electrolytes, local wound care, and physiotherapy)
Grade 2	Requires pharmacologic treatment with drugs other than listed in grade 1, blood transfusions, or total parenteral nutrition
Grade 3	Requires surgical, endoscopic, or radiological intervention
Grade 4	Life-threatening complication with/ without intensive care unit management
Grade 5	Death

8.4 Adverse Events Related to Study Procedures

AEs and SAEs caused by the study specimen collections (e.g. bruising, bleeding) will be reported each time blood is collected for the study. No intestine will be removed for the purposes of the study and no surgery will be altered by participation in the study. AE information will be obtained by direct monitoring of the study subject by clinician observation by the care team, and self-reporting by the study subject or his/her guardian(s).

AEs related to study procedures will be followed until resolution or until 48 hours after study initiation or until discharge from the hospital, whichever comes first. Resolution of an AE is defined as the return to pretreatment status or stabilization of the condition with the expectation that it will remain chronic.

8.5 Follow Up of Events of Special Interest, Complications, and SAEs

All events of special interest, complications and AEs related to study procedures will be monitored through the electronic health record.

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested to elucidate the nature and/or causality of the event as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated event data within 24 hours of receipt of the information.

8.6 Reporting of Events of Special Interest, Complications, and AEs

Reporting will be completed via an Electronic Data Collection Tool

- The primary mechanism for reporting a complication, events of special interest, or AEs related to study procedures will be the electronic data collection tool in the protocol specific Duke RedCAP database.
- If the Duke RedCAP is unavailable, then the investigator will enter the complications, events of special interest, or AEs related to study procedures into the electronic system as soon as it becomes available.

9 CLINICAL MONITORING

This study does not provide intervention to the patient that has the potential to cause harm. Enrolled patients are receiving metronidazole as part of their treatment plan. However, the study will collect information regarding the presence of harmful clinical events that occur as a result of metronidazole infusion.

The electronic medical record will be searched for blood, urine, and tissue cultures in the postoperative period to monitor for infectious complications and noted in the CRF.

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Considerations

Sample size is derived to meet the primary objective of characterizing the PK of metronidazole in plasma and the intestinal wall of infants. As per FDA guidance, 20 infants will provide > 80% power to target a 95% confidence interval within 60% and 140% of the geometric mean estimates of metronidazole clearance and volume of distribution, assuming a coefficient of variation of up to 40%[16]. This will also provide >80% power to identify a 20% difference in plasma and intestinal wall concentrations of metronidazole and its primary metabolite 2-hydroxymetronidazole using a paired t-test at an alpha of 0.05. Because the study requires participation from the subject only during time of surgery, dropout rates should be low, and operative cancellations will be replaced.

10.2 Analysis Plan

Population for Analysis
All enrolled participants with at least 1 evaluable PK sample will be included in the PK analysis and all participants who receive at least 1 dose of study metronidazole will be included in the safety analysis population.

Statistical Methodology
Descriptive statistics, such as number of observations, mean, median, 95% CI, standard deviation, standard error, minimum, and maximum, will be presented by age cohort for continuous variables (such as height, weight, and BMI percentile). Other descriptive statistics, such as counts, proportions, and/or percentages, will be presented by age cohort group to summarize discrete variables (such as race and sex).

Demographics, Baseline Characteristics, and Clinical Course
The number of participants completed and discontinued early from study, and the reasons for discontinuation, will be summarized. Demographic and baseline characteristics will also be summarized. Variables include race, age, sex, ethnicity, and other selected clinical variables will be recorded prior to initiation of study drug. Variables including drug dosing and other selected clinical variables during study drug administration will be recorded.

Safety and Clinical Laboratory Analyses
Laboratory data (serum BUN, serum creatinine, potassium, sodium, AST, ALT, total bilirubin, albumin, prealbumin, ESR, CRP, serum WBC count, Hg, Hct, platelet, PT, PTT) will be tabulated by age cohort. Continuous laboratory measurements will be described using univariable descriptive statistics (mean, median, etc.); observed values and changes from baseline will be summarized. Lab tests reflective of electrolyte abnormalities (e.g., hyponatremia, hypokalemia) will be further summarized in terms of the most extreme values and largest changes from baseline (in the appropriate direction) observed from start of study drug through the end of therapy.

Adverse events and events of special interest will be summarized by age cohort and relationship to drug exposure will be explored. Prior and concomitant medications will be summarized by World Health Organization (WHO) drug class.

PK Analysis

Population PK analysis using non-linear mixed effects modeling (NONMEM VII software) will be used to estimate population PK parameters and their variance for both plasma and intestinal PK. The influence of covariates (i.e. postnatal age, gestational age, etc.) on PK parameters will be explored. Post-hoc Bayesian individual PK parameters will then be estimated for each subject. The plasma and intestinal concentrations-time profiles of metronidazole will be presented in figure form by subject and cohort as well as plasma to intestine concentration. Descriptive statistics will be presented for continuous and categorical variables. A detailed description of population PK analyses can be found in the PK analysis plan.

11 PARTICIPANT CONFIDENTIALITY

The principal investigator will ensure that the use and disclosure of protected health information obtained during this research study complies with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule. The rule provides U.S. federal protection for the privacy of protected health information by implementing standards to protect and guard against the misuse of individually identifiable health information of participants participating in clinical trials. “Authorization” is required from each research participant (i.e., specific permission granted by an individual to a covered entity for the use or disclosure of an individual’s protected health information). A valid authorization must meet the implementation specifications under the HIPAA Privacy Rule. Authorization will be combined in the informed consent document (approved by the IRB).

Participants will have code numbers and will not be identified by name. Participant confidentiality is held strictly in trust by the participating investigators, their staff, and the sponsor(s), and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests, in addition to the clinical information relating to participating participants.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitors or other authorized representatives of the sponsor may inspect all documents and records required to be maintained by the investigator. This documentation includes, but is not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. Clinical study sites will permit access to such records.

12 INFORMED CONSENT PROCESS

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation in this study will be provided to the participants' families. Consent forms describing in detail the study procedures and risks are given to the participant's legal guardian, and written documentation of informed consent is required prior to enrolling in the study. Consent forms will be IRB-approved, and the participant's legal guardian will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the participant's legal guardian and answer any questions that may arise. The participant's legal guardian will sign the informed consent document prior to the participant being enrolled in the study. The participant's legal guardian may withdraw consent at any time throughout the course of the study. A copy of the informed consent document will be given to the participants' legal guardian for their records. The rights and welfare of the participants will be protected by emphasizing to their legal guardians that the quality of their medical care will not be adversely affected if they decline to participate in this study.

Site staff may employ IRB-approved recruitment efforts prior to the participant consenting. However, before any protocol-specific procedures are performed to determine protocol eligibility, an informed consent form must be signed. By signing the informed consent form, the participant's legal guardian agrees that the participant will complete all evaluations required by the trial, unless the participant is withdrawn voluntarily or is terminated from the trial for any reason.

13 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

A CRF will be used to record all participant data. The CRF will be used for the recording of all historical participant information and study data as specified by this protocol. The CRF must be completed by designated and trained study personnel. The CRF will be signed by the principal investigator.

According to ICH E6 source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). Source documents are defined as original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial).

It will be the responsibility of the investigator(s) to ensure that the study file at the site is maintained. The study file will contain, but will not be limited to:

- Current investigator's brochure and all previous versions
- Study protocol
- Protocol amendments (if applicable)
- Manual of operations (if applicable)
- Informed consent form (blank)
- Signed informed consent forms
- Revised informed consent forms and/or all addenda (blank)
- DHHS number for IRB or other documentation of IRB compliance with FDA regulations (if applicable)
- Documentation of IRB approval of protocol, consent form, any protocol amendments, and any consent form revisions.
- Annual IRB updates and approvals
- All correspondence between the investigator and IRB

The site will maintain appropriate medical and research records for this trial, in compliance with ICH E6, Section 4.9, and regulatory and institutional requirements for the protection of confidentiality of participants. The site will permit authorized representatives of the sponsor, its designees, and appropriate regulatory agencies to examine (and, when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress. These representatives will be permitted access to all source data, which include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, participants' memory aid or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and participant files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial. Data collection forms will be derived from the CRFs.

14 QUALITY CONTROL AND QUALITY ASSURANCE

The principal investigator will provide direct access to all trial-related sites, source data/documents, data collection forms, and reports for the purpose of monitoring and auditing by the safety monitor, and inspection by local and regulatory authorities. The principal investigator will ensure that all study personnel are appropriately trained, and applicable documentations are maintained on site.

15 ETHICS/PROTECTION OF HUMAN PARTICIPANTS

15.1 Ethical Standard

The investigator will ensure that the study will be conducted in accordance with U.S. federal regulation 21 CFR Part 50, 45 CFR Part 46 and 21 CFR Part 312.60-69, as specified on the signed form FDA 1572, applicable state laws, and the International Conference on Harmonization: Good Clinical Practice: Consolidation Guideline. The investigator is responsible for informing the IRB of any safety issues related to the study and the study drug, including reports of SAEs, if required. The institution must also have a Federal Wide Assurance to perform the trial.

15.2 Institutional Review Board

Prior to enrollment of participants into this trial, the protocol, the informed consent form, and any materials or advertisements presented to participants will be reviewed and approved by the appropriate IRB constituted according to FDA regulations and be registered with OHRP. Should amendments to the protocol be required, the amendments will be written by the sponsor and provided to the investigator for submission to the IRB. Participants will not be compensated by the sponsor for their participation in this study.

15.3 Informed Consent

The investigator will choose participants in accordance with the eligibility criteria detailed previously. The investigator will not exercise selectivity so that bias is prevented. In this study, participants' legal guardian will sign one IRB-approved informed consent form for study enrollment. All participants' guardian must sign an informed consent form that complies with the requirements of both 21 CFR Part 50 and Health Insurance Portability and Accountability Act (HIPAA) before entering the trial. A consent form that complies with the requirements of 21 CFR Part 50 and a separate HIPAA-compliant authorization form for the use and disclosure of the participant's protected health information may be used instead, per institutional standard operating procedures. For details regarding the informed consent process, see Section 12.

15.4 Study Discontinuation

If the study is discontinued by the safety monitor or principal investigator, enrolled participants will continue to be followed for safety assessments for 48 hours (See Section 8).

16 DATA HANDLING AND RECORD KEEPING

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. Data collection forms will be derived from paper or electronic CRFs. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Data reported in the CRF should be consistent with the data collection form/source documents, or the discrepancies should be documented.

16.1 Data Management Responsibilities

All data collection forms, and laboratory reports must be reviewed by the clinical team and data entry staff, who will ensure that they are accurate and complete. AEs related to study procedures and complications must be graded, assessed for severity and causality, and reviewed by the site principal investigator or designee. During the study, the investigator must maintain complete and accurate documentation for the study.

16.2 Types of Data

Data for this study will include safety, laboratory [e.g., PK data], and surgical outcome measures.

16.3 Study Records Retention

Records and source documents pertaining to the conduct of the studies (i.e. including CRFs, data collection forms when used as source, electronic medical records, consent forms, laboratory test results and study product accountability records), must be retained by the investigator for 5 years after the end of the study. Study information in a subject's medical records will be retained forever.

16.4 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or requirements of the manual of procedures. The noncompliance may be on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with the following sections of the ICH guidance for Good Clinical Practice:

4.5. Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
5.1. Quality Assurance and Quality Control, section 5.1.1
5.2. Noncompliance, sections 5.20.1, and 5.20.2

It is the responsibility of the site to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation or within 5 working days of the scheduled protocol-required activity. All deviations must be promptly reported to the sponsor.

All deviations from the protocol must be addressed in study data collection forms. A completed copy of the protocol deviation form must be maintained in the regulatory file. Protocol deviations must be submitted to the local IRB/IEC per their guidelines.

16.5 Participant Privacy/Authorization

The principal investigator will ensure that the use and disclosure of protected health information obtained during a research study complies with the HIPAA Privacy Rule. The rule provides U.S. federal protection for the privacy of protected health information by implementing standards to protect and guard against the misuse of individually identifiable health information of participants participating in clinical trials. Authorization is required from each research participant (i.e., specific permission granted by an individual to a covered entity for the use or disclosure of an individual's protected health information). A valid authorization must meet the implementation specifications under the HIPAA Privacy Rule. Authorization will be combined in the informed consent document (approved by the IRB).

17 LITERATURE REFERENCES

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DUKE UNIVERSITY HEALTH SYSTEM

Consent To Participate In A Research Study

Minor Consent
Perioperative Tissue Penetration of Antimicrobials in Infants

Concise Summary

The purpose of this study is to see how an antibiotic used during surgery, called metronidazole, is processed in the blood and tissue of infants having intestinal surgery and whether the dose given is enough to help prevent infections after surgery.

If you agree for your child to participate, blood samples will be obtained from intravenous lines placed for the surgery. Blood will be collected at the end of antibiotic infusion, and then at 30, 60 and 90 minutes after infusion. Additional blood will be collected at the time of surgery and at the end of the surgery. The amount of blood collected will be about 5 mL (1 teaspoon) total. No additional needle sticks or intravenous lines will be required for your child to be involved in this study. In addition, a small piece of tissue will be taken from the intestine after it's removed.

The samples will be analyzed to see how much metronidazole is found in the blood at each timepoint, and in the tissue post-surgery.

To minimize risk to your child, we have limited the volume of blood that we will draw to approximately 5 mL in total.

Please let the study doctor or study team know if you are interested in learning more about this study as explained in the remainder of this consent form.

You are being asked to allow your child to participate in this research study because he/she is undergoing intestinal surgery. Research studies are voluntary and include only people who choose to take part. Please read this consent form carefully and take your time in making your decision. Your child's study doctor or study staff will discuss this consent form with you. Please ask about any words or information that you do not clearly understand.

This consent form describes the nature of the study, risks, inconveniences, discomforts, and other important information about the study. It is important that you ask questions about what is required for participation in this research study. We encourage you to talk with your family and friends before you decide to allow your child to take part in this research study.

Please tell the study doctor or study staff if your child is taking part in another research study.

WHO WILL BE MY CHILD'S DOCTOR ON THIS STUDY?

If you decide to allow your child to participate, Dr. Elisabeth Tracy or Dr. Sarah Commander will be your child's doctor for the study and will be in contact with your child's regular health care provider throughout the time that your child is in the study and afterwards, if needed.

DUKE UNIVERSITY HEALTH SYSTEM

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WHY IS THIS STUDY BEING DONE?

The purpose of this study is to see how an antibiotic used during surgery, called metronidazole, is processed in the blood and tissue of infants having intestinal surgery and whether the dose given is enough to help prevent infections after surgery.

HOW MANY CHILDREN WILL TAKE PART IN THIS STUDY?

Up to 20 children at Duke University Medical Center will participate in this study.

WHAT IS INVOLVED IN THIS STUDY?

If you agree to allow your child to participate, you will be asked to sign and date this consent form. The surgeon will perform surgery as part of your child's standard of care. Enrolling your child in this study will not affect his or her hospital care in any way.

As part of your child's routine care, a needle will be placed into a vein (called an "intravenous line") in your child's arm or leg in order to collect blood during the hospital stay. This means that the intravenous lines will need to be placed even if your child is not involved in this study.

Your child will also be given an antibiotic called metronidazole as part of the routine care prior to surgery.

While your child is undergoing surgery, blood samples will be obtained from these intravenous lines. No additional needle sticks or intravenous lines will be required for your child to be involved in this study.

If you agree for your child to participate, blood samples will be obtained from intravenous lines placed for the surgery. Blood will be collected at the following timepoints:

- End of antibiotic infusion
- 30 minutes post-infusion
- 60 minutes post-infusion
- 90 minutes post-infusion.
- At the time of surgery
- At the end of the surgery

The amount of blood collected will be about 5 mL (1 teaspoon) total. No additional needle sticks or intravenous lines will be required for your child to be involved in this study.

In addition, a small piece of tissue will be taken from the intestine after it's removed.

The samples will be analyzed to see how much metronidazole is found in the blood at each timepoint, and in the tissue post-surgery.

DUKE UNIVERSITY HEALTH SYSTEM

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HOW LONG WILL MY CHILD BE IN THIS STUDY?

Your child's direct participation in the study will last for the duration of his or her surgery at Duke University Health System (DUHS), however their medical records may be reviewed by the research staff for at least one month afterwards.

You can choose to stop your child's participation at any time without penalty or loss of any benefits to which your child is entitled. However, if you decide to stop your child's participation in the study, we encourage you to talk to your child's doctor first.

WHAT ARE THE RISKS OF THE STUDY?

As a result of your child's participation in this study, he/she has the following risks. You should discuss these with the study doctor and your child's regular health care provider if you choose.

Loss of confidentiality:
We will be collecting information from your child's medical record for this study. We will only collect information that is directly related to the study and every effort will be made to keep your child's information confidential; however, there is the potential risk of loss of confidentiality.

Risks of Blood Drawing:
No additional needle sticks will be performed to draw blood for research. To minimize risk to your child, we have limited the volume of blood that we will draw to approximately 5 mL (about 1 teaspoon) in total.

There may be risks that are not yet known.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

There is no direct benefit to your child from participating in this research study. This study will provide valuable information that may eventually help us to better prevent infections in infants undergoing intestinal surgery in the future.

WILL MY CHILD'S INFORMATION BE KEPT CONFIDENTIAL?

Participation in research involves some loss of privacy. We will do our best to make sure that information about your child is kept confidential, but we cannot guarantee total confidentiality. Your child's personal information may be viewed by individuals involved in this research and may be seen by people including those collaborating, funding, and regulating the study. These may include representatives from the Duke Cancer Research Institute and representatives of the Thrasher Research Fund – Medical Research for Children. We will share only the minimum necessary information in order to conduct the research. Your child's personal information may also be given out if required by law.

As part of the study, your child's records may be reviewed in order to meet federal or state regulations. Reviewers may include representatives of the Duke University Health System Institutional Review

Board, and Office for Human Research Protections. If they review your child's research record, they may also need to review your child's entire medical record.

The doctors taking care of your child will document in the medical record that your child is participating in this study. Results of tests and studies done solely for this research study and not as part of your child's regular care will not be included in your child's medical record. Any research information in your child's medical record will be kept indefinitely.

The study results will be retained in your child's research record forever. Any research information in your child's medical record will also be kept indefinitely.

While the information and data resulting from this study may be presented at scientific meetings or published in a scientific journal, your child's identity will not be revealed.

Some people or groups who receive your child's health information might not have to follow the same privacy rules. Once your child's information is shared outside of DUHS, we cannot guarantee that it will remain private. If you decide to share private information with anyone not involved in the study, the federal law designed to protect your child's health information privacy may no longer apply to the information you have shared. Other laws may or may not protect sharing of private health information.

WHAT ARE THE COSTS?
There are no costs to you for participating in this study. You or your insurance provider will be responsible and billed for all costs related to your child's routine medical care, including copayments and deductibles. Routine medical care services are those that your child would have received for their condition if your child were not participating in this research study.

WHAT ABOUT COMPENSATION?
You or your child will not receive compensation for your child's participation in this study.

WHAT ABOUT RESEARCH RELATED INJURIES?
Immediate necessary medical care is available at Duke University Medical Center in the event that your child is injured as a result of participation in this research study. However, there is no commitment by Duke University Medical Center, Duke University Health System, Inc., or your child's Duke University Medical Center physicians, to provide monetary compensation or free medical care to your child in the event of a study-related injury.

For questions about the study or a research-related injury, contact Dr. Tracy at 919-681-5077 during regular business hours and at pager number 919-970-9649 after hours and on weekends and holidays.

WHAT ABOUT MY RIGHTS TO DECLINE PARTICIPATION OR WITHDRAW MY CHILD FROM THE STUDY?

You may choose to not allow your child to be in the study, or, if you agree to the study, you may withdraw your child from the study at any time. If you withdraw your child from the study, no new data about your child will be collected for study purposes. Data and samples already collected for the study cannot be withdrawn.

Your decision not to allow your child to participate, or to withdraw from the study will not involve any penalty or loss of benefits to which your child is entitled, and will not affect your child's access to health care at Duke University Medical Center. If you do decide to withdraw your child, we ask that you contact Dr. Tracy in writing and let her know that you are withdrawing from the study. Dr. Tracy's mailing address is DUMC, Box 3815, Durham, NC 27710.

We will tell you and your child about new information that may affect your child's health, welfare, or willingness to stay in this study.

Your child's doctor may decide to take your child off this study if your child's condition gets worse, if your child has serious side effects, or if your child's study doctor determines that it is no longer in your child's best interest to continue. If this occurs, you will be notified and your child's study doctor will discuss other options with you and your child.

Your child's samples and/or data may be stored and shared for future research without additional informed consent if identifiable private information, such as your child's name and medical record number, are removed. If your child's identifying information is removed from their samples or data, we will no longer be able to identify and destroy them.

The use of your child's samples may result in commercial profit. You and your child will not be compensated for the use of the samples other than what is described in this consent form.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or a research-related injury, or if you or your child have problems, concerns, questions or suggestions about the research, contact Dr. Tracy at 919-681-5077 during regular business hours and at pager number 919-970-9649 after hours and on weekends and holidays.

For questions about your child's rights as a research participant, or to discuss problems, concerns or suggestions related to the research, or to obtain information or offer input about the research, Duke University Health System Institutional Review Board (IRB) Office at (919) 668-5111.

DUKE UNIVERSITY HEALTH SYSTEM

Consent To Participate In A Research Study

Minor Consent
Perioperative Tissue Penetration of Antimicrobials in Infants

STATEMENT OF CONSENT

The purpose of this study, procedures to be followed, risks and benefits have been explained to my child and me. I have been allowed to ask questions, and my questions have been answered to my satisfaction. I have been told whom to contact if I have questions, to discuss problems, concerns, or suggestions related to the research, or to obtain information or offer input about the research. I have read this consent form and agree for my child to be in this study, with the understanding that I may withdraw my child at any time. We have discussed the study with my child (if over age 6), who agrees to be in the study. I have been told that I will be given a signed and dated copy of this consent form.

_____	_____	_____
Signature of Parent or Legal Guardian	Date	Time
_____	_____	_____
Signature of Person Obtaining Consent	Date	Time