Institutional Review Board
Informed Consent Document for Research

Study Title: Dexmedetomidine Opioid Sparing Effect in Mechanically Ventilated Children (DOSE Trial)
Version Date: 30 SEPTEMBER 2019

Part 1 of 2: MASTER CONSENT

Name of participant: _____ Age: _____

We are asking your child to be a part of a research study. The study is being done at more than one hospital, so the information about the study is divided into two parts. Part 1 is called the Master Consent. It has information about the study that applies to all of the hospitals in the study. Part 2 has information about the study that is only for the hospital where your child will treated. We must give you both parts to give you important information about the study.

CONCISE SUMMARY

We are asking your child to take part in a research study and asking your permission to allow him/her to join the study. Once you learn more about the study, you can make a decision about whether or not to allow your child to take part. Before you decide, it is important for you to understand why the research is being done and what it means to be in the research study. If you decide to take part, we will ask you to sign this form.

Your decision for your child to take part in this study is voluntary. This means you are free to decide if you want your child to be in the study. We are asking your child to be in the study because he/she needs pain medicine and also needs a breathing machine while in the intensive care unit. Children who are on a breathing machine in the intensive care unit are usually given a drug called fentanyl to treat pain. But fentanyl can be addictive and children can have withdrawal effects when the medicine is stopped. This study will test whether adding another medication, dexmedetomidine, will reduce the amount of fentanyl needed while your child is on the breathing machine. Every child in the study will get regular pain medicine. They will also receive either the study drug or the placebo (fluid with no drugs in it). If your child joins the study, he/she might not get the study drug. Approximately 75% of the participants will receive the study drug and 25% will receive the placebo.

Your child will receive either fentanyl with the study drug (dexmedetomidine) or fentanyl with saline placebo for up to 7 days. The study doctors will follow your child for a total of up to 28 days. A detailed description of what happens in the study is explained later in this form.

Side effects (bad reactions to the drug) may occur from taking the study drug. The side effects range from very common to rare. A detailed list of possible side effects is provided later in this document. There may

not be any benefits to your child for being in this study. We hope the information learned from this study will help other children in the future.

This document may contain words and information that you do not understand. Please ask your study doctor or study staff to explain anything that is not clear to you. Please take time to read all the information carefully and talk about it with friends and relatives if you wish. Ask the research doctor or staff to explain anything that is not clear or if you have any questions. Take time to decide whether or not to volunteer to have your child take part in this research study.

What is the purpose of this study?
Fentanyl is a medicine doctors use to treat pain, but long term use can result in dependence. Some patients experience withdrawal when the medicine is stopped. Fentanyl is approved by the U.S. Food and Drug Administration (FDA) in children who are at least 2 years old for short-term use with surgical procedures, to help reduce pain and to help children sleep after some surgeries. This study will test whether adding another medication, dexmedetomidine, will reduce the amount of fentanyl needed while your child is on the breathing machine. Dexmedetomidine is not approved by the FDA for use in children. The amount of study medication used in this study are within the dose ranges that have been given to children.

This study is paid for by a grant from the National Center for Advancing Translational Sciences (NCATS), a part of the National Institutes of Health (NIH). Kanecia Zimmerman, MD and Christoph Hornik, MD of Duke University are the main study doctors (Principal Investigators). Duke University is using funds from the grant to pay your child's study doctor and his or her research staff to conduct the study.

About 48 children at about 20 hospitals will be in this study. All of the hospitals in this study are in the United States.

You do not have to agree to let your child be in this research study. If your child is not a part of the study, he/she will still get the healthcare and medicines that are needed to treat his/her condition. If you agree to let your child be in the study now but change your mind later, you can stop participating at any time. You will need to tell the study doctors that you do not want your child to be in the study any more. Also, if we learn something new that may affect the possible risks or benefits of this study, you will be told so that you can decide whether or not you still want your child to be in this study.

What will happen and how long will you be in the study? / What would I need to do if I join the study?
If you decide to allow your child to join the study, you will be asked to sign and date this consent form. After you sign, these are the things we will ask you to do:

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Screening Visit (up to 7 days before receiving study drug)
We will:

- Talk about your child's medical history, including their sex, date of birth, age, race, and current medical condition.
- Review all medicines, including all over-the-counter and herbal products your child may have taken 48 hours before starting study drug.
- Discuss any changes in your child's medical condition or any problems your child may be having.

Baseline Visit (up to 7 days after Screening Visit):
We will:

- Complete this visit as early as the same day as the Screening Visit or up to 7 days after the Screening Visit.
- Review and update any new medical history that was not known at the Screening Visit.
- Complete a physical exam, including height and weight.
- Review and record the pain and sleep scores that your nurses or doctor will complete within the 24 hours before your child begins the study.
- Review and record the settings on the machine used to help your child's breathing.
- Review and record laboratory results that were taken as part of your child's usual care.

Group Assignment:
Each child in this study will receive a medicine that is commonly used to treat patients who are on a breathing machine. This medicine- fentanyl- will be ordered by the doctor taking care of your child in the intensive care unit (ICU). The medicine will help to prevent pain and help your child sleep.

In addition to the fentanyl, children in this study will be put in one of four groups. One group (about 1 out of 4 children in the study) will be given a saline placebo (fluid with no drugs in it). The other 3 groups (about 3 out of 4 children in the study) will get the study drug. We will use a computer to decide which group your child will be in. We will not tell you, the study doctors or nurses which group your child is in. Only the pharmacist who is preparing the medication will know if your child is getting the study drug or placebo.

Treatment Visits (up to 7 days after the assigned treatment is started)
We will:

- Give your child either the study drug or placebo intravenously (IV) through a small plastic tube that is placed in your child's vein. Your child already needs an IV for his or her care, so there is no need for any additional needle sticks as part of this study.
- Gather information about any medicines your child is taking.

- Record pain and sleep scores at least twice a day.
- Take up to 2 blood draws each day, totaling about ¼ teaspoon, to show how well the body processes and eliminates the fentanyl and study drug.
- Review and record any changes in your child's medical condition or any problems your child may be having.

Short-Term Follow-up (up to 28 [+/- 2] days or discharge from the ICU – whichever comes first)
Daily assessments will be completed for 7 days after your child has completed treatment. Two additional assessments will be completed 7 days and 14 days later. All assessments will be finished by Day 28 or sooner.
At this visit we will:

- Review and update information on the medicines your child is taking.
- Record information about whether your child is having any signs of medication withdrawal.
- Review and record any changes in your child's medical condition or any problems your child may be having.
- Record any lab test results that may be related to any side effects of the medicines.
- The study staff will record the date the breathing machine was no longer required and the date of ICU discharge.

Your child's participation in the study will end when he/she is discharged from the ICU or up to 28 days from the first day of study drug, whichever comes first.

Side effects and risks that you can expect if your child takes part in this study:
More common side effects of fentanyl include:

- Sleepiness
- Feeling sick to your stomach
- Trouble going to the bathroom
- Slower heartbeat
- Lower blood pressure
- Dry mouth

Less likely side effects of fentanyl include:

- Seizures
- Seeing, hearing, or feeling things that are not there
- Pounding in the ears
- Shaking of the hands or feet

Withdrawal Side Effects of fentanyl can include:

- Sweating
- Chills
- Muscle aches
- Stomach pain, and upset
- Trouble sleeping
- Nervousness
- Irritation

More common possible side effects of Dexmedetomidine:

- Lower heart rate
- Lower blood pressure
- Higher blood pressure
- Sleepiness

Less likely possible side effects of Dexmedetomidine:

- Confusion
- Feeling sick to your stomach
- Dry mouth
- Elevated temperature

Risks of Drawing Blood:
Risks associated with drawing blood from your child's arm include momentary discomfort and/or bruising. Infection, excess bleeding, clotting, or fainting are also possible, although unlikely.

Risks that are not known:
Your child may experience unknown risks and problems related with the use of the study drug, including allergic reaction to this medicine or a bad effect because the study drug is taken at the same time as another medication. Whenever someone takes any new medications, there is a risk that an allergic reaction may occur. Such reactions can be serious or fatal. If your child suffers from allergies to medications, food products, or environmental elements, please tell the study doctor now.

Good effects that might result from this study:
We do not know if your child will benefit from being in this study. However, the information learned from the study may help other children in the future who require pain medication and help with their breathing.

Reasons why the study doctor may take your child out of this study:

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The study doctor may take your child out of the study at any time. The reason why they would remove your child from the study could be because your child had an unexpected reaction, needs different type of treatment, or because the study rules change. If the study doctor takes your child out of the study, you will be asked complete all of the final clinical visits and laboratory tests.

What will happen if you decide to stop being in this study?
If you decide to stop being part of the study, please tell your child's study doctor. Stopping will not change your child's regular medical care in any way. We will tell you if we learn anything new that might change your mind about being in the study. If your child leaves the study, no new data about your child will be collected for study purposes unless the data are about a bad effect related to the study. If this occurs, we may need to review your child's entire medical record. All data that have already been collected for the study, and any new information about a bad effect related to the study, will be sent to the study sponsor.

Privacy:
We will collect and share health information about your child from their medical and research records. The kinds of information that will be collected and shared are:

- Medical records (office, clinic, or hospital) and pharmacy records
- Laboratory test results, medicines, diagnoses
- Pain, sleep, and mental status scores

The health and study information listed above may be shared with the following groups:

- Duke University/Duke Clinical Research Institute (DCRI)
- University of Utah, Utah Trial Innovation Center, Data Coordinating Center
- Johns Hopkins University, Safety Review
- Federal government research and health organizations (FDA, NIH, NCATS)
- Vanderbilt University Medical Center, the Institutional Review Board (IRB) overseeing this study

We protect your child's information from disclosure to others to the extent required by law. We cannot promise complete secrecy.

We may publish the results of this research. However, we will keep your child's name and other identifying information confidential.

Study results will be kept in your child's research record for at least 3 years after the study funding from NIH has ended. At that time either the research information not already in your child's medical record

will be destroyed or information identifying your child will be removed from the study results. Any research information in your child's medical record will be kept indefinitely.

CAN I GET A COPY OF MY CHILD'S MEDICAL RECORDS?

You have a right to see and make copies of your child's medical records. However, to ensure the reliability of the study, you will not be able to see or copy your child's records related to the study until the sponsor has completed all work related to the study. At that time, you may ask to see the study doctor's files related to your child's participation in the study, and you may ask the study doctor to correct any study-related information about your child that is wrong.

This study is paid for by the National Institutes of Health (NIH). Because of this, your child's study information is protected by a Certificate of Confidentiality. This Certificate allows us, in some cases, to refuse to give out your child's information even if requested using legal means.

It does not protect information that we have to report by law, such as child abuse or some infectious diseases. The Certificate does not prevent us from sharing your child's information if we learn of possible harm to your child or others, or if your child needs medical help.

Clinical Trials Registry.
A description of this clinical trial will be available on www.clinicaltrials.gov, as required by U.S. Law. This website will not include any information that can identify your child. At most, the website will include a summary of the results. You can search this website at any time.

At the end of the study, all records will continue to be kept in a secure location for as long a period as required. All study databases will have personal information removed and will be stored at the University of Utah Trial Innovation Center, Data Coordinating Center.

Study Results:
When the study is over, we will place what we learned from the study on the study website for you to see.