Study Title:	A Phase 0 / Phase 1 Trial of Metformin for Premature Infants with Bronchopulmonary Dysplasia
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Children's Wisconsin
INTRODUCTION TO THE INFORMED CONSENT

Name of Subject: _____

A Phase 0 / Phase 1 Trial of Metformin for Premature Infants with Bronchopulmonary Dysplasia
Phase 0 Permission Form

G. Ganesh Konduri, MD, MS
Pediatrics - Neonatology
(414) 266-6820
Medical College of Wisconsin
999 N. 92nd Street Suite 410
Milwaukee, WI 53226

Subject: You are invited to take part in this research. This form tells you why this project is being done, what will happen in the project, possible risks and benefits to you, your choices, and other important information. If there is anything that you do not understand, please ask questions. Then you can decide if you want to join this project or not. If you are under the age of 18, your parent or guardian also needs to give their permission for you to join this project.

Parent/Guardian: Your child is invited to take part in this research. This form tells you why this project is being done, what will happen in the project, and possible risks and benefits to your child. If there is anything you do not understand, please ask questions. Then you can decide if you want your child to join this study or not. The word "you" in this form refers to your child.

Definitions

CW – Children's Wisconsin
IRB – Institutional Review Board
Bronchopulmonary Dysplasia (BPD)– A chronic lung condition related to prematurity; diagnosed when a premature infant needs respiratory support at 36 weeks corrected gestational age
Premature – born before the end of the full term of pregnancy
Corrected Gestational Age – the age of a premature infant adjusted to account for how early they were born
Metformin – a type of drug that has been used to treat diabetes and metabolic syndromes in adults and children

Purpose

This project is being done to determine if a medication called metformin will help prevent a lung condition called bronchopulmonary dysplasia, or BPD, in premature infants.

Length

- You will be in this research project for about 2 months.
- You will receive metformin for three, or seven or fourteen days.
- We will collect information about your hospitalization from your medical chart when you are discharged.

Procedures

You will receive the study drug twice a day for three or seven or fourteen days. It will be given at the time of your feeding, either through your feeding tube or in your bottle.

List of visits:

- Baseline Visit/Enrollment
  - Total Number: 1
  - Total Time: 1 hour
- Study Drug Administration
  - Total Number: 6 or 14 or 28
  - Total Time: 3 or 7 or 14 days
- Study Drug Discontinuation
  - Total Number: 1
  - Total Time: 24 hours

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Procedures that will occur at various visits:

Invasive Procedures

- Blood sample collection

Non-invasive Procedures

- Study drug administration
- Urine sample collection
- Data collection from medical record

Risks

This is a brief list of the most commonly seen side effects. The ***full consent form*** after this introduction contains a more complete list of potential research risks.

Drug risks:

- Hypoglycemia (low blood sugar)
- Feeding intolerance
- Metabolic acidosis
- Renal failure
- Liver dysfunction
- Infection

Study Risks:

- We are very careful to protect you and your privacy. Still, there is a chance that some of your information could be seen by someone outside of this study team.

Benefits

We don't know if this project will help you. Your condition may get better but it could stay the same or even get worse.

My Other Options

You do not have to join this project. Your other options may include:

- Joining a different project
- Routine care for this condition
- Getting no treatment for this condition

If you have more questions about this project at any time, you can call Dr. Konduri at 414-266-6820.

If you have questions about your rights as a participant, want to report any problems or complaints, or offer input, you can call the MCW/Froedtert Hospital Research Subject Advocate at 414-955-8844 or Children's Wisconsin Human Research Protection Program Office at 414-337-7133.

CONSENT TO PARTICIPATE IN RESEARCH

A1. INTRODUCTION – WHY ARE WE ASKING YOU TO PARTICIPATE?

You are being invited to participate in this research because you were born at less than 29 weeks gestational age, are now between 8- and 22-weeks postnatal age and have been diagnosed with a lung condition called bronchopulmonary dysplasia, or BPD. Infants are diagnosed with BPD if they need respiratory support at 36 weeks corrected gestational age. We are investigating whether metformin administration in premature infants will help prevent or lessen the severity of BPD. In this phase of the study, we will be looking at how older premature infants tolerate metformin by checking blood levels of the drug and monitoring them for side effects such as low blood sugar, feeding intolerance, and infection.

A total of about 40 people are expected to participate in this research, all at Children's Wisconsin. We plan to enroll 10 infants into this phase of the study

The Director of the project is Dr. Ganesh Konduri in the Department of Pediatrics, Neonatology. A research team works with Dr. Konduri. You can ask who these people are.

The research study is funded by Advancing Healthier Wisconsin Endowment..

A2. DO I HAVE TO PARTICIPATE?

You can decide whether to take part in this research or not. You are free to say yes or no. If you do not agree to join, or if you leave, you will not be penalized or lose any benefits that you had before starting the research project. Even if you join this project, you do not have to stay in it. You may stop at any time. Take as much time as you need to make your choice.

A research project is different from routine medical care in three ways: 1) there are extra risks that we will tell you about in this form; 2) you may have some extra medical tests and visits; 3) the research procedures, tests and visits follow a set plan that must be kept.

A3. WHY IS THIS PROJECT BEING DONE?

In this study, we want to find out more about the side effects (problems and symptoms) of metformin, an investigational drug for bronchopulmonary dysplasia, or BPD, and what doses of metformin are safe for infants to take. Everyone in this study will receive metformin, which is considered experimental in infants, but it is approved by the U.S. Food and Drug Administration for older children and adults. We do not know all the ways that this drug may affect premature infants. This study is not likely to help you, but we hope the information from this study will help us develop a better treatment for BPD in the future.

B1. WHAT WILL HAPPEN IF I PARTICIPATE?

If you decide to join the research study, the following things will happen:

1. Your eligibility to be in the study will be confirmed by the study team.

2. If you are eligible for the study, you will be participating in one of the 4 groups of babies among the ten babies as shown in the table below. The group you are assigned to wil be based on the progress of the research study.
3. The number of doses and amount of study medication will depend on the group you are in, as shown below in the table. The amount and number of doses you will receive is marked below in the table.

Group	Sample size	Dose	Total daily dose	Duration	This is the Group You are in
1	2	2.5mg/kg twice a day	5mg/kg/day	3 days	
2	2	5mg/kg twice a day	10mg/kg/day	3 days	
3	3	10mg/kg twice a day	20mg/kg/day	7 days	
4	3	12.5mg/kg twice a day	25mg/kg/day	14 days	

4. You will be given a metformin dose twice a day for three, seven or fourteen days, for a total of 6, 14 or 28 doses of the study drug. Metformin will be given with your feedings, either through a feeding tube or a bottle.

5. We will monitor the level of metformin in your blood, as well as your blood sugar and lactic acid levels. To do this, we will collect a blood sample at one hour, four hours, and 12 hours after you receive the first dose of metformin. The blood sample will be collected from either an existing central line, by a venipuncture (needle stick to a vein), or by a heelstick. If you are in group 4, 3 extra blood samples will be collected, after 2 weeks of study medication. We will try to draw these samples at the same time as your regular clinical labs, but this will not always be possible.

6. Any extra blood that was sent to Children's Wisconsin lab as part of your regular medical care during your hospital stay that is left over after routine tests are completed will be collected and also checked for metformin, glucose and lactic acid levels.

7. After you receive the last dose of metformin, we will collect a urine sample every 6 hours for 24 hours to check metformin levels in your body as well as lactic acid levels. This will be done by either placing a cotton ball in the diaper or by using a urine collection bag, which is a bag with a small amount of adhesive on it that sticks to the skin.

8. While you are receiving metformin, we will collect information from your chart, including the results of blood tests that are done as part of your routine medical care, respiratory support, and other medications you are receiving.

9. After you have finished the course of metformin, we will continue to monitor you for a week for any side effects.

10. If you have severe side effects, the study drug will be stopped and will not be started again.

11. We will collect information from your medical record about your hospital stay in the NICU when you are discharged.

Information that can identify you will not be attached to your blood and urine samples. The samples collected for this part of the project will be coded, which means it will be labeled with numbers and/or letters instead of information that could identify you. Only the research team will be able to link the code to you. The research team will make every effort to protect the information and keep it confidential, but it is possible that an unauthorized person might see it. Depending on the kind of information being collected, it might be used in a way that could embarrass you.

It is against federal law (Genetic Information Nondiscrimination Act, or GINA) for health insurance companies to deny health insurance, or large employers to deny jobs, based on your genetic information. But the same law does not protect your ability to get disability, life, or long-term care insurance.

B2. HOW LONG WILL I BE IN THE PROJECT?

You will be in this research for about 2 months.

You will be given metformin for 3, 7 or 14 days.

B3. CAN I STOP BEING IN THE PROJECT?

You are free to withdraw from the project at any time. If you leave, your regular medical care will not change. If you are thinking about leaving, please tell the research doctor.

The research doctor can tell you about the effects of stopping, and you and the research doctor can talk about what follow-up care would help you the most.

The research doctor may take you out of this project at any time for any reason, including if:
- They think it is in your best interest.
- You do not follow the project rules.
- The whole project is stopped.

If this happens, the research doctor will tell you.

C1. WHAT HEALTH RISKS OR PROBLEMS CAN I EXPECT FROM THE PROJECT?

There are risks to taking part in any research project. There is a risk that you may get a dose of a drug that does not help your condition or may make it worse. There also may be problems (side effects) we do not know about yet, from metformin itself, or how it combines with other drugs you are taking. If we learn about new important side effects, we will tell you.

We watch everyone in the project for problems (side effects). **You need to tell the research doctor or a member of the research team immediately if you experience any problems, side effects, or changes in your health.**

C2. RISKS OF METFORMIN

The research drug, metformin, itself may cause problems (side effects). Side effects may be mild or very serious. Some can last a long time or never go away.
Many go away soon after you stop taking metformin. Drugs can affect individuals in different ways. Complications of some of the side effects below may lead to life-threatening events such as low glucose or acid build up in the body or infection. These complications may be worse if you have liver or kidney failure and can possibly lead to death.

The side effects that will monitor for include:

1. Feeding intolerance: this means you are not digesting your feedings well; it can be shown by stomach looking very full, vomiting, or having undigested milk or formula left in your stomach at the time of your next feeding. If your feedings decrease in amount by more than half or your feedings need to stop completely because you are not tolerating them, we may stop the study drug.

2. Hypoglycemia, or low blood sugar: if your blood glucose level decreases to less than 50, metformin will be stopped.

3. Metabolic acidosis: this is a condition in which too much acid builds up in the blood. This can occur if the kidneys do not remove enough acid from the blood, there is too much acid being produced, or there is not enough bicarbonate in the blood, which helps neutralize acid.

4. Kidney or liver failure: this is not a side effect of metformin, but if you develop kidney or liver failure, we will stop this study drug.

C3. OTHER RISKS OF THIS RESEARCH PROJECT

Other procedures that are part of the research also involve some risks:

- Risk of blood sample collection: the side effects that you might experience as a consequence of having a blood sample collected include possible discomfort and bruising at the site of the blood draw. Every precaution will be taken to assure your personal safety and minimize discomfort.

- Unknown risks: there may be side effects that no one knows about yet. The researchers will tell you if they learn anything that might change your mind about participating in the study.

Another risk may be loss of confidentiality. Every effort will be made to keep your research records confidential but we cannot guarantee it. Depending on the kind of information being collected, it may be embarrassing if your research information were accidentally seen. If you have questions, you can talk to the project director about whether this could apply to you.

C5. ARE THERE ANY BENEFITS TO TAKING PART IN THE PROJECT?

This study is not likely to help you, but we hope the information from this study will help us develop better treatments for BPD.

D1. ARE THERE ANY COSTS TO BEING IN THE PROJECT?

Some of the medical care that you will receive in this project is considered routine care for your condition and would be recommended whether or not you join the project. Costs for routine care will be billed to you or your insurance carrier. For routine clinical care, you will be responsible for paying any copayment, coinsurance, or deductible that is required by your insurance carrier. Activities / costs that are part of the project will not be billed to you or your insurance company. These are study drug administration, blood samples for metformin and lactic acid levels, and urine metformin and lactic acid levels. If you have questions regarding costs, please contact Dr. Konduri.

If you participate in this research, the costs of any necessary emergency medical treatment in the event of a research-related injury will be billed to you or your health insurance.

D2. WILL I BE PAID FOR PARTICIPATING IN THE PROJECT?

There is no payment for being in this research study.

D3. WHAT OTHER HEALTHCARE CHOICES DO I HAVE?

You do not have to join this project. You are free to say yes or no. If you do not join this project, your research doctor can discuss other healthcare choices with you.
Whether or not you join this project, your usual medical services will not change.
The research doctor can explain both the possible benefits and the risks of other options that are available to you.

D4. WILL I BE GIVEN NEW INFORMATION ABOUT THE PROJECT?

If we learn any important new information metformin that might change your mind about being in the project, we will tell you about it right away. You can then decide if you want to stay in the project.

When research biospecimens are collected and analyzed, there is the chance of finding something clinically relevant. There may be benefits to learning such results (such as early detection and treatment of a medical condition), but there are risks as well (such as feeling worried about a finding for which no treatment is required or appropriate).

In this study, you will be informed of any findings of possible clinical significance that may be discovered during review of results from your research. Clinical samples collected to check your glucose and lactate levels, will be available to your care team and we will inform you of the results and any treatment needed, but you will not be informed of the results from your research biospecimens. The results of your research biospecimens will not be placed in your medical record.

The results from the biospecimens we collect in this research study are not the same quality as what you would receive as part of your health care. The biospecimens will be reviewed by a physician who normally reads such results. We will provide you with this information so that you may discuss it with your primary care physician.

D5. WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THE PROJECT?

Emergency medical treatment for injuries caused by your participation in this research project will be arranged for you. You or your health insurance may be billed for the costs of this emergency treatment. If your research-related injury requires medical care beyond this emergency treatment, you or your insurer may be responsible for the costs of this follow-up care.

At this time, there is no plan for any additional financial payments.

If you believe that you have been injured because of your participation in this project, contact the research doctor right away. Contact information: Dr. Ganesh Konduri, 414-266-6820.

Nothing in this consent form affects any legal rights you may have nor does it release the investigator, the sponsor, the institution, or its agents from liability for negligence.

D6. WHO CAN ANSWER MY QUESTIONS ABOUT THE PROJECT?

- If you have more questions about this project at any time, you can call Dr. Ganesh Konduri at 414-266-6820.
- If you have questions about your rights as a research participant, want to report any problems or complaints, or offer input, you can call the MCW/Froedtert Hospital Research Subject Advocate at 414-955-8844 or Children's Wisconsin Human Research Protection Program at 414-337-7133.

E. PERMISSION TO COLLECT, USE AND SHARE HEALTH INFORMATION

E1. What health information will be collected and used for this study?

To be in this research project, the study team needs your permission to access, collect and use some of your health information. If you say no, you cannot be in the study. This information may come from questions we ask, forms we ask you to fill out, or your medical record, as described below. We will only collect and use information needed for the project.

The protected health information (PHI) originates from services you will or have received at one or more of the following locations: the Medical College of Wisconsin (MCW); Versiti, Inc.; Children's Wisconsin (CW); any Froedtert Health Affiliate- Froedtert Hospital (FH), Inc.; Froedtert Menomonee Falls Hospital; Froedtert West Bend Hospital; Froedtert & The Medical College of Wisconsin Community Physicians Clinics, Inc. (FMCWCP); the West Bend Surgery Center, LLC; and the Froedtert Surgery Center, LLC.

The health information to be collected and used for this project is:

- Demographic and identifying information such as name, birth date, birth weight, gender, race, and gestational age.
- Clinical data from medical records, including medical history, respiratory support, vital signs, medications, lab results, growth and feeding information, and the clinical course of your hospital stay.
- All tests and procedures that will be done in the study, including study drug administration and lab results.

E2. Who will see the health information collected for this project?

The only MCW/CW employees allowed to handle your health information are those on the research team, those on the Institutional Review Board (IRB) and those who check on the research activities to make sure the hospital's rules are followed.

If the costs of any necessary emergency medical treatment in the event of a research-related injury are billed to your health insurance, your health information may need to be disclosed to the insurer for billing purposes.

The research team may share your information with people who don't work at MCW/CW because they planned, pay for, or work with us on this project. The federal Privacy Rule may no longer protect your health information once it leaves MCW/CW. For this project, we plan to share information with those doctors, researchers or government representatives working with us on this project at the institutions or companies listed here:

National Institute of Health, Bethesda, MD

Because this project involves the use of drugs and/or devices, the FDA also has the right to inspect all study records.

We may record your research information, including results of tests and procedures done for research, in your Children's Wisconsin medical record. As a result, this research information may be seen by people allowed to see your medical records for healthcare operations or treatment, by those you allow to see your medical records by giving written permission, and by others when required by law.

A copy of this signed consent/assent and HIPAA authorization will be placed in your Children's Hospital medical record.

We will not use your personal health information for a different project without your permission or the permission of a hospital research review board (IRB). Once all personal identification is removed from your health information and biospecimens, the information and biospecimens may be used for future research or distributed to another investigator for future research without additional informed consent from you or your legally authorized representative. The information might also be used or released for other purposes without asking you. Results of the project may be presented in public talks or written articles, but no information will be presented that identifies you.

E3. What are the risks of sharing this health information?

One risk of taking part in a research project is that more people will handle your personal health information collected for this project. The research team will make every effort to protect the information and keep it confidential, but it is possible that an unauthorized person might see it. If you have questions, you can talk to the research team.

E4. How long will you keep the health information for this project?

If you sign this form, we plan to keep your information for 10 years after the research study ends in case we need to check it again for this project.

E5. Can I cancel my permission to share this health information?

If you change your mind later and do not want us to collect or share your health information, you need to send a letter to Dr. G. Ganesh Konduri at 999 N. 92nd Street, Suite 410, Milwaukee, WI, 53226. The letter must say that you have changed your mind and do not want the researcher to collect and share your health information. At that time, we may decide that you cannot continue to be part of the project. We may still use the information we have already collected.

F1. For more information about the project

A description of this clinical trial will be available on http://www.ClinicalTrials.gov as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

You can look up this project by referring to the ClinicalTrials.gov number NCT07120971 or by asking the research team for a printed copy.

CONSENT/ASSENT TO PARTICIPATE

By signing my name below, I confirm the following:

- I have read (or had read to me) this entire consent document. All of my questions have been answered to my satisfaction.
- The project's purpose, procedures, risks and possible benefits have been explained to me.
- I agree to let the research team use and share the health information and other information gathered for this project.
- I voluntarily agree to participate in this research project. I agree to follow the procedures as directed. I have been told that I can stop at any time.

IMPORTANT: You will receive a signed and dated copy of this consent form. Please keep it where you can find it easily. It will help you remember what we discussed today.

Assent of Minor Subject (17 years old or younger)	
Documentation of Assent *Documentation is not specific to a cursive signature and may include whatever the child's mark is*	**Date**
If child's assent is not obtained above, please indicate reason below (check one): ☐Assent is documented on a separate IRB-approved assent form ☒ Child is under the IRB-approved age range for assent ☐The IRB granted a waiver of assent, please specify:_____	

Consent of Parent(s)/Guardian(s) of Minor Subject		
Name of Parent/Guardian *please print*	**Signature of Parent/Guardian**	**Date**

Name of Second Parent/Guardian *please print*	**Signature of Second Parent/Guardian**	**Date**

If the signature of the second parent/guardian cannot be obtained, please indicate the reason:

☐ Second parent/guardian is deceased
☐ Second parent/guardian is not reasonably available
☐ Second parent/guardian is incompetent
☐ Only one parent/guardian has legal responsibility for the care and custody of the minor
☐ Other _____

*** Name of person discussing/ obtaining consent** *please print*	**Signature of person discussing/obtaining consent**	**Date**

Name of Principal Investigator *please print* __ I participated in consent process __ I acknowledge enrollment of this subject into the project	**Signature of Principal Investigator**	**Date**