CONSENT TO ACT AS A PARTICIPANT IN A RESEARCH STUDY

Protocol Title:	Physiological-based Pharmacokinetics Approach to Determine the Extent of Drug Exposure of Antiseizure Medications During Pregnancy and Breastfeeding
Protocol	**PBPK**
Protocol Version / Date:	**Version 3: 6/10/2022**

Principal Investigator:	Page B. Pennell, MD	**Telephone:**	412-802-6642
Emergency Contact:	Kerry Oddis	**Telephone:**	412-692-4918
Participant ID Number:			

SUMMARY OF KEY INFORMATION ABOUT THIS STUDY

TITLE: Physiological-based Pharmacokinetics Approach to Determine the Extent of Drug exposure of Antiseizure Medications During Pregnancy and Breastfeeding

PRINCIPAL INVESTIGATOR (Study Doctor): Page Pennell, MD
Phone Number 412-802-6642

You are being asked to join a clinical research study. This summary contains important information to help you decide if you want to join the study or not. A more detailed description of procedures and risks are provided within the Main ICF.

PURPOSE:

This project focuses on anti-seizure medication (ASM) clearance and physiological factors in pregnant women with epilepsy

DURATION:

This clinical research study involves approximately 6 visits.

- Preconception
- 1st Trimester
- 2nd Trimester
- 3rd Trimester
- Birth
- 6-12 weeks postpartum

PROCEDURES:

If you decide to participate, you will be asked to have physical examinations, blood draws and collection of urine.

RISKS:

Potential risks include pain and rare instances of localized bleeding, bruising, infection and/or fainting from the needle sticks required to obtain blood samples.

If you have any questions about any of the possible risks or discomforts listed above, you should talk to your study doctor or your regular doctor.

BENEFITS:

You may not benefit from being in this clinical research study. This study will help us learn how to optimize dosing of LTG and LEV during pregnancy and postpartum

ALTERNATIVES:

You may choose not to participate in this study or participate in another study if one is available. This is a voluntary research study. You do not have to join the study. Even if you decide to join now, you can change your mind later. Please ask the study doctor if you have any questions about the study or about this summary.

END OF CONSENT SUMMARY

About this consent form

Please read this form carefully. It tells you important information about a research study. A member of our research team will also talk to you about taking part in this research study. People who agree to take part in research studies are called "subjects." This term will be used throughout this consent form.

The University of Pittsburgh Medical Center is made up of UPMC hospitals, health care providers, and researchers. In the rest of this consent form, we refer to the University of Pittsburgh Medical Center system simply as "UPMC."

If you have any questions about the research or about this form, please ask us. Taking part in this research study is up to you. If you decide to take part in this research study, you must sign this form to show that you want to take part. We will give you a signed copy of this form to keep.

Please note: A description of this research study will be available at www.ClinicalTrials.gov as required by U.S. Law. This website will not include information that can identify you. At most, the Website will include a summary of the results. You can search this Web site at any time.

Why is this research study being done?

Most women with epilepsy have normal pregnancies but appear to be at risk for problems during pregnancy (e.g., seizures, change in medications, depression, c-sections) and adverse outcomes in their children (e.g., thinking or behavioral problems). The purpose of this observational study is to establish the risk and determine the factors or contributions to those risks.

Women with epilepsy who are pregnant or planning pregnancy are being enrolled in this project. You cannot participate in another clinical trial at the same time you participate in this study.

You will be one of approximately 60 women and their children to participate in this study at UPMC.

The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) is paying for the study to be done.

Voluntary Participation

Your participation in this research study is entirely voluntary. You may want to discuss this study with your family, friends and/or your personal physician before agreeing to participate. If there are any words you do not understand, feel free to ask us. The investigators will be available to answer your current and future questions.

Whether or not you provide your consent for participation in this research study will have no effect on your current or future relationship with the University of Pittsburgh. Whether or not you provide your consent for participation in this research study will have no effect on your current or future medical care at a UPMC hospital, affiliated health care provider or your current or future relationship with a health care insurance provider.

As both your doctor and a research investigator, s/he is interested both in your medical care and the conduct of this research study. Before agreeing to participate in this research study, or at any time during your study participation, you may discuss your care with another doctor who is not associated with this research study. You are not under any obligation to participate in any research study offered by your doctor.

How long will I take part in this research study?

You participation will require 6 visits, beginning at preconception and ending around 6-12 weeks postpartum.

What will happen in this research study?

Visit 1: Enrollment-Preconception

During the enrollment visit, you will review your eligibility for this study and the informed consent form. Following this process, you will be asked to answer questions regarding demographic information, socioeconomic status, family history, OB/Gyn history, medical history, seizure history, and medications for seizures, all other medications both prescribed and purchased over the counter, herbal products and dietary supplements including vitamins. Additionally, you will be asked to complete the anti-seizure medication (ASM) side effect questionnaire. Physical and neurological exams with vitals will be performed.

You will be shown how to use a paper diary to record your ASM use, including the dose and time, missed doses, as well as seizure frequency and type. We will ask that you record this information from the time that you enroll in the study until the end or your participation, approximately 3 months after your baby is born.

After positive pregnancy test

Following a positive pregnancy test, you will have a home visit by the study physician's assistant (PA). Study staff will call you before the first home visit to review instructions for a 24-hour urine collection. During the home visit, the study PA will train you on how to obtain a blood sample using the volumetric absorptive microsampling (VAMS) kit which includes detailed

instructions on how to collect blood from a finger prick. The VAMS device is FDA approved and is being used for its approved purpose. The amount of blood is approximately less than 1/5 of a teaspoon. You will be asked to perform VAMS collections in your home beginning at pregnancy diagnosis and approximately every 2 weeks for a total of 3 times during the first trimester. If you feel you are not able to do this comfortably, the PA can return to your home to help you with the VAMS collections. If you feel you are unable to use the VAMS device, the PA will obtain the blood sample via venipuncture (phlebotomy). The study PA will take the first VAMS and 24-hr urine sample with them. Telephone or virtual visits will occur monthly throughout pregnancy with the research PA, with review of the diary data and collection of the ASM Side Effect Questionnaire.

Visits 2-4: Trimesters 1-3

You will have one study visit in person each trimester during pregnancy with the research PA and/or doctor. Samples will be collected at each study visit, including urine and blood via venipuncture (phlebotomy) for antiseizure medication concentration, hormones, and creatinine measurements. The amount of blood drawn will be approximately 2 tablespoons. A brief neurological exam will be performed. You will be asked to fill out a survey about any possible medication side effects. The study staff will review your daily diary entries about your seizures and medications.

Visit 5: Birth

The study coordinator will obtain about 2 tablespoons of blood from the umbilical cord after it has been cut; the samples will be obtained from the side attached to the placenta and not your baby. Approximately 2 tablespoons of your blood will be collected by venipuncture as close to the timing of delivery as possible. The study staff will also perform a brief neurological examination and you will be asked to fill out the survey about medication side effects. These will be performed at a time that is convenient and does not interfere with your obstetric care.

Visit 6: 6-12 Weeks Postpartum

One week after delivery, you will be asked to perform the VAMS collections again at home and repeat this at 2 weeks and 3 weeks after delivery (total of 3 times). You will be asked to fill out the survey on the same day as the VAMS collections. You will return for a postpartum study visit at 6-12 weeks following delivery, with review of the daily diary entries, brief neurological exam, a survey about medication side effects, collection of blood and urine samples (approximately 2 tablespoons), and additional review of obstetric and newborn outcomes. The sex of the baby will be verified.

If you are nursing, you will be asked if you wish to provide breastmilk samples at home, using an electric or manual breast pump throughout a 24-hour period. The breastmilk can be stored in your refrigerator for up to 72 hours, and you will bring the refrigerated samples with you to your visit 6.

OPTIONAL GENETIC SAMPLING, STORAGE, AND FUTURE USE

We plan to do genetic research on the DNA and RNA in you and your child's tissue samples. DNA is the material that makes up your genes. All living things are made of cells. Genes are the part of cells that contain the instructions which tell our bodies how to grow and work, and determine physical characteristics such as hair and eye color. Genes are passed from parent to child. We may also perform a whole genome analysis on your DNA sample. Often researchers study just a few areas of your genetic code that are linked to a disease or condition. In whole genome studies, all or most of your genes are analyzed and used by researchers to study links to epilepsy and its treatments. Blood for genetic studies will be collected at your first study visit.

We will also ask you if you are willing for us to obtain a genetic sample from your child by an infant heelstick to collect less than 1/5 of a teaspoon of blood. If the heelstick is not successful, we will use a buccal swap to obtain the DNA sample.

The National Institutes of Health (NIH), who is funding this study, requests that we share the genetic samples collected as part of this study with other researchers. This is known as Genomic Data Sharing. This information will be stored and shared through an NIH controlled access database. This means that data will be available only to select groups of people approved by an NIH committee.

The database includes all kinds of genomic data from this and other studies funded by the NIH. Genomic studies, including genome-wide association studies (GWAS), look at genetic differences in the entire human genome (the complete set of human genes). Researchers look at these genetic differences to better understand certain health conditions and diseases. Your samples, genomic data and health information will be stored and shared with other researchers. The samples and information will be available for any research question, such as research to understand what causes certain diseases (for example heart disease, cancer, or psychiatric disorders), development of new scientific methods, or the study of where different groups of people may have come. They also want to save the remainder of your (and your child's) samples for future research. Your individual genomic data and health information will be put in a controlled-access database. This means that only researchers who apply for and get permission to use the information for a specific research project will be able to access the information. Your genomic data and health information will not be labeled with your name or other information that could be used to identify you. Researchers approved to access information in the database will agree not to attempt to identify you.

There is no additional physical risk to you or your child to obtain the genetic samples. You and your child have already provided these samples when you had blood drawn early in the study. You will be told of any changes in the way the study is done and of any risks to you.

There may be risks to your privacy and the privacy of your relatives from storing your information in the repository. Although the NIH takes measures to protect your privacy, we

believe the chance that your and your child's identities could become re-connected with your genetic and health information is very small, but we cannot make guarantees. If your or your child's genetic information were re-identified, personal information about you and your child, your and your child's health, and your and your child's risk of disease could become known to others. This could present unknown risks. Your privacy and the confidentiality of your and your child's data are very important to us; we will make every effort to protect them.

Current federal law called the Genetic Information Non-Discrimination Act, or GINA, will help protect you from genetic discrimination in health insurance and employment. This law helps to lower the risk of health insurance or employment discrimination. The law does not include other types of misuse by life insurance or long-term care insurance. To learn more about the GINA Law, please ask the study staff or check the internet.

_____ Yes, I agree to participate and to allow my child to participate in the genetic sampling in this project.

_____ Yes, I agree to allow my child's genetic sample to be stored and used in future studies. Even if you initially agree to participate, later you can have your child's sample destroyed if you change your mind and decide you do not want to participate by notifying your study doctor in writing.

_____ Yes, I agree to participate but DO NOT allow my child to participate in the genetic sampling in this project.

____ Yes, I agree to allow the investigators to share a portion of my genetic sample with the NIH genetic database investigators and to be used in future studies. If you agree to the genetic database sharing, you cannot have your sample destroyed if you change your mind and decide you do not want to participate because there will be no way of identifying your sample. If you later change your mind you can have the remainder of your sample withdrawn from future use by notifying your doctor in writing.

_____ No, I do not want myself or my child to participate in the genetic sampling in this project. If you decide to withdraw your remaining samples, you should contact the study staff in writing to:

Kerry Oddis / Dr. Page Pennell
University of Pittsburgh
Department of Neurology
Kaufmann Medical Building
3471 Fifth Avenue, Suite 810
Pittsburgh, PA 15213

Future Participation

The researchers may want to contact you after your participation in this project ends. They may want to get more information or perform more procedures for this project or they may want to ask you to participate in another project. You should indicate below whether or not you agree to allow the study staff to contact you for these reasons by placing an "X" by the appropriate statement.

Your answer will not affect your ability or anyone else's to participate in this study. If you change your mind at any time, please contact the study staff.

_____ I agree to allow the study staff to contact me if they need more information from me for this study or if they would like to offer me participation in another project.

_____ I do not want the study staff to contact me after I finish participating in this study.

Sending Study Information to Research Collaborators Outside UPMC

We will send your study information to research collaborators at the University of Minnesota. Employees who are overseeing proper study conduct may look at your study records. No personal identifiable information will be available in the data collected, as it will be coded with an alphanumeric code that will not be linked to your name or personal details. No personally identifying information is requested on the diary website or paper diary, and subjects should not enter identifying information. If entered, the subject will be requested to change the information to non-identifying information. We will label all your study materials with a code instead of your name. The key to the code connects your name to your study information and samples. The study doctor will keep the key to the code here at UPMC and will not share it with our research collaborators. No one outside of UPMC will know which study information or samples are yours.

What are the risks and possible discomforts from being in this research study?

Potential risks include pain and rare instances of localized bleeding, bruising, infection and/or fainting from the needle sticks required to obtain blood samples from you. The umbilical cord sample will be obtained after the cord is cut and will not pose any discomfort or danger to your newborn. Your baby may experience some pain, rare instances of bruising, and/or infection from the heel stick procedure. Side effects and problems not listed above and not expected at this time may occur. You will be told of any changes in the way the study is done and of any risks to you or your child.

Data and records collected on subjects in connection with this research project will be held confidential unless specifically required to be disclosed by state or federal law. Their records

will become part of their hospital charts and study file books. They will not be personally identified in any publication that may come from this project.

What are the possible benefits from being in this research study?

This study is not designed to benefit you directly. The study results may be used to help others in the future.

Can I still get medical care with UPMC if I don't take part in this research study, or if I stop taking part?

Yes. Your decision won't change the medical care you get within MGB now or in the future. There will be no penalty, and you won't lose any benefits you receive now or have a right to receive.

Taking part in this research study is up to you. You can decide not to take part. If you decide to take part now, you can change your mind and drop out later. We will tell you if we learn new information that could make you change your mind about taking part in this research study.

What should I do if I want to stop taking part in the study?

If you take part in this research study, and want to drop out, you should tell us. We will make sure that you stop the study safely. We will also talk to you about follow-up care, if needed. It is possible that we will have to ask you to drop out before you finish the study. If this happens, we will tell you why. We will also help arrange other care for you, if needed.

Will I be paid to take part in this research study?

You will get paid for each completed study visit as noted in the following table:

Visit 1 (Enrollment-Preconception)	$75
Visit 2 (1st Trimester)	$50
6 weeks GA VAMS	$25
9 weeks GA VAMS	$25
12 weeks GA VAMS	$25
Visit 3 (2nd Trimester)	$50
Visit 4 (3rd Trimester)	$50
Visit 5 (Birth)	$75
Week 1 Postpartum VAMS	$25
Week 2 Postpartum VAMS	$25
Week 3 Postpartum VAMS	$25
Breastmilk collection	$75
Infant heelstick via VAM or Buccal swab	$50
Visit 6 (6 weeks -3 months Postpartum)	$50

Total	$625

If you do not finish the study, you will not be paid for the visits you have not completed. Payment will be made via check for each study visit, and will be received after the respective study visit has been completed. You will receive $625 total, if you complete all study visits.

All compensation is taxable income to the participant regardless of the amount. If a participant receives $600 or more in a calendar year from one organization, that organization is required by law to file a Form 1099 – Miscellaneous with the IRS and provide a copy to the taxpayer. Individuals who do not provide a social security number may still participate in the research, but the IRS requires that 28% of the payment be sent by the institution to the IRS for 'backup withholding;' thus you would only receive 72% of the expected payment.

What will I have to pay for if I take part in this research study?

All study related activities will be paid for by the sponsors & Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD).

Although study funds will pay for certain study-related items and services, NICHD will not pay for services that are considered routine clinical care. UPMC will bill your health insurer for, among other things, routine items, and services you would have received even if you did not take part in the research. This includes blood work to measure hormones and drug levels for your clinical care. You will be responsible for payment of any deductibles and co-payments required by your insurer for this routine care or other billed care. If you have any questions about costs to you that may result from taking part in the research, please speak with the study doctors and study staff. If necessary, we will arrange for you to speak with someone in Patient Financial Services about these costs.

What happens if I am injured as a result of taking part in this research study?

If you believe that the research procedures have resulted in an injury to you, immediately contact the Principal Investigator who is listed on the first page of this form. Emergency medical treatment for injuries solely and directly related to your participation in this research study will be provided to you by the hospitals of UPMC. Your insurance provider may be billed for the costs of this emergency treatment, but none of those costs will be charged directly to you. If your research-related injury requires medical care beyond this emergency treatment, you will be responsible for the costs of this follow-up care. At this time, there is no plan for any additional financial compensation. You do not, however, waive any legal rights by signing this form.

If I have questions or concerns about this research study, whom can I call?

You may call us with your questions or concerns. Our telephone numbers are listed below. Ask questions as often as you want.

Page B. Pennell, MD is principal investigator of this research study. You can call her at, 412-802-6642 Monday through Friday, 8:30 AM-4:30 PM. You can also call the study coordinator Kerry Oddis at 412-692-4918, Monday through Friday, 8:00 AM-4:00 PM or via email kmoddis@upmc.edu with questions about this research study.

If you have a medical emergency, you should contact your neurologist, obstetrician/gynecologist, or pediatrician as you normally would, keeping in mind that this is an observational study and does not change your treatment during this study.

If you have questions about the scheduling of appointments or study visits, call the study coordinator at 412-692-4918.

If you have any questions about your rights as a research subject or wish to talk to someone other than the research team, please call the University of Pittsburgh Human Subjects Protection Advocate toll-free at 866-212-2668.

Significant financial conflict of interest

If an investigator has a significant financial conflict of interest, the conflict must be disclosed to the research participants, consistent with the COI Management Plan developed by the investigators with advice from the COI office, and approved by the IRB.

If I take part in this research study, how will you protect my privacy?

Federal law requires UPMC to protect the privacy of health information that identifies you. In the rest of this section, we refer to this information simply as "health information."
In this study, we may collect health information about you from:

- Past, present, and future medical records
- Research procedures, including research office visits, tests, interviews, and questionnaires

Certificate of Confidentiality for Health Information and Other Identifying Information from the Research

In this research study, we have obtained a Certificate of Confidentiality from the Department of Health and Human Services (DHHS). By granting the Certificate, DHHS is not approving the research itself, but is helping us strengthen the privacy protections for your health information and other identifying information from the research. With the Certificate, we cannot be forced (for example by court order or subpoena) to disclose your health information or other identifying information from the research in any Federal, State or local civil, criminal, administrative, legislative, or other proceedings. (Note that information that is not from the

research, such as existing hospital or office health records, is protected by general privacy law but does not receive the Certificate's stronger protection. The Certificate also does not prevent you or a member of your family from voluntarily releasing any information about yourself or your involvement in this research study.)

Why Health Information and other identifying information from the research might be used or shared, and by/with whom

Even with these privacy protections, your health information and other identifying information from the research may still be used within UPMC by the researchers and the staff involved in this research study, by the UPMC ethics board that oversees the research, and by other staff within UPMC who need the information to do their jobs (such as for treatment, payment (billing) or health care operations such as overseeing the quality of care or research). Your information may also be shared by these groups with others outside of UPMC for certain purposes as follows.

We may use and share your information with:

- The sponsor(s) of the research study, and people or groups it hires to help perform this research study
- Other researchers and medical centers that are part of this research study and their ethics boards
- A group that oversees the data (study information) and safety of this research
- People or groups that we hire to do certain work for us, such as data storage companies, insurers, and lawyers
- Federal and state agencies (such as DHHS and agencies within DHHS like the Food and Drug Administration, the National Institutes of Health, and the Office for Human Research Protections), with other U.S. or foreign government bodies, and with organizations that provide independent accreditation and oversight of hospitals and research. For example, disclosure may be necessary upon request of DHHS for an audit, program evaluation, or investigation. Disclosure may also be necessary if required by the federal Food, Drug, and Cosmetic Act or its regulations.
- A public health or public safety authority, or with specific individuals who may be at risk of harm, if we learn information that could mean harm to you or others. When state mandatory reporting statutes would require us to disclose information, including about child or elder abuse, we will voluntarily disclose that information.
- The University of Pittsburgh Office of Research Protection
- UPMC hospitals or other affiliated healthcare providers

You should know that the recipients of these reports may use this information as they see fit, and may end up sharing the information with other government agencies. We may also voluntarily disclose information in other situations where you or others are at risk. In order to minimize disclosures for treatment, payment, or health care operations purposes, information from this research study will not be placed in your medical record. Some people or groups outside UPMC who get your health information or other identifying information from the research might not have to follow the same privacy rules that we follow. We share your information only when we must, and we ask anyone who receives it from us to protect your privacy. However, once your information is shared outside UPMC, we cannot promise that it will remain private.

Because research is an ongoing process, we cannot give you an exact date when we will either destroy or stop using or sharing your health information. The protections of the Certificate of Confidentiality and other UPMC privacy protections will continue to apply to your health information and other identifying information from the research for as long as our researchers keep the information. The results of this research may be published in a medical book or journal or used to teach others. However, your name or other identifying information will not be used for these purposes without your specific permission. Although every reasonable effort has been taken, confidentiality during Internet communication activities cannot be guaranteed and it is possible that additional information beyond that collected for research purposes may be captured and used by others not associated with this study. Per University of Pittsburgh policy, all research records must be maintained for at least 7 years following final reporting or publication of a project. For projects involving children, records must be maintained for 5 years past age of majority (age 23 per PA State law) after study participation ends.

Your Privacy Rights

You have the right not to sign this form that allows us to use and share your health information for research, however, if you don't sign it, you can't take part in this research study.

You have the right to withdraw your permission for us to use or share your health information for this research study. If you want to withdraw your permission, you must notify the person in charge of this research study in writing. Once permission is withdrawn, you cannot continue to take part in the study.

If you withdraw your permission, we will not be able to take back information that has already been used or shared with others. The Certificate of Confidentiality and other MGB privacy protections will continue to apply to your health information and other identifying information from the research that our researchers keep.

You have the right to see and get a copy of your health information that is used or shared for treatment or for payment. To ask for this information, please contact the person in charge of this research study. You may only get such information after the research is finished.

VOLUNTARY CONSENT

The above information has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask questions about any aspect of this research study during the course of this study, and that such future questions will be answered by a qualified individual or by the investigator(s) listed on the first page of this consent document at the telephone number(s) given. I understand that I may always request that my questions, concerns, or complaints be addressed by a listed investigator.

I understand that I may contact the Human Subjects Protection Advocate of the IRB Office, University of Pittsburgh (1-866-212-2668) to discuss problems, concerns, and questions; obtain information; offer input; or discuss situations in the event that the research team is unavailable.

By signing this form, I consent to participate in this research study and provide my authorization to share my medical records with the research team. A copy of this consent form will be given to me.

_____ _____

Participant's Signature Date

_____

Printed Name of Participant

<u>Minor Subject's Parental Permission/Assent</u>

_____

Participant's (Child's) Name (Print)

I understand that, as a minor (age less than 18 years), the above-named child is not permitted to participate in this research study without my consent. Therefore, by signing this form, I give my consent for his/her participation in this research study.

_____ _____

Parent's or Guardian's Name (Print) Relationship to Participant (Child)

_____ _____

Parent's or Guardian's Signature Date

VERIFICATION OF EXPLANATION:

I certify that I have carefully explained the nature and purpose of this research to the above-named adolescent-subject in age-appropriate language. He/she has had an opportunity to discuss it with me in detail. I have answered all of his/her questions, and he/she provided affirmative agreement (i.e., assent) to participate in this research.

_____ _____

Investigator Signature Date

CERTIFICATION OF INFORMED CONSENT

I certify that I have explained the nature and purpose of this research study to the above-named individual(s), and I have discussed the potential benefits and possible risks of study participation. Any questions the individual(s) have about this study have been answered, and we will always be available to address future questions, concerns, or complaints as they arise. I further certify that no research component of this protocol was begun until after this consent form was signed.

_____ _____

Printed Name of Person Obtaining Consent Role in Research Study

_____ _____

Signature of Person Obtaining Consent Date