CONSENT TO TAKE PART IN RESEARCH

Dartmouth-Hitchcock Medical Center

Biomarkers in chemotherapy-induced peripheral neurotoxicity: Better tools and understanding

Victoria Lawson, MD, Harold Swartz, MD, & Mary Chamberlin, MD

Introduction: You are being asked to take part in a research study. Taking part in research is voluntary.

You are being asked to take part in this study because you are scheduled to begin chemotherapy. Your decision whether or not to participate in this research will have no effect on the type or quality of your medical care.

Taking part in a research study is not the same as getting regular medical care. The purpose of regular medical care is to improve your health. The purpose of a research study is to gather information to help patients in the future.

Please ask questions if there is anything about this study you do not understand.

What is the purpose of this study?

The purpose of the study is to learn about chemotherapy-induced peripheral neurotoxicity (CIPN). CIPN is a common and potentially severe result of chemotherapy, which can cause patients to experience symptoms such as numbness, tingling, pain, and sometimes weakness as a result of nerve damage from chemotherapy. It is very difficult to predict who is at the greatest risk to develop CIPN, and our current measures are not able to identify the disease at an early stage. In this study, we will test a novel method of measuring and predicting CIPN. The technique, called electron paramagnetic resonance (EPR) oximetry, uses injected India ink (medical tattoo) to sense oxygen and tell us about the oxygen levels in your tissue. Levels of oxygen in your tissue may be an early sign of CIPN. Changes in your tissue oxygen levels will be measured over the course of your cancer treatment, and the results will be compared with standard, neurological tests for CIPN.

We are also testing blood samples for a biomarker called neurofilament light chain (NF-L). This biomarker has been elevated in blood samples from other neurodegenerative diseases. We will be testing to see if this is also elevated in blood samples from those who develop CIPN.

Will you benefit from taking part in this study?

You might not personally benefit from being in this research study. We hope to gather information that may help people in the future.

What does this study involve?

Your participation in this study may last up to twelve months, or for the entire duration of your chemotherapy treatment. We will ask you to return to the clinic for at least three visits after signing this informed consent document. The visit schedule is provided below. Please note that it is possible to divide each study visit into multiple, shorter appointments if needed.

Visit 1a: Consent, India ink injection, and Neurological exam (Approximately 2 Hours)

- Review and sign consent form.
- Before beginning chemotherapy, one of the participating physicians will inject a small amount of black India ink (approximately one drop) just under the skin of your foot. India ink is the same ink used for tattoos, and will make a small, permanent spot at the injection site about the size of an eraser head. Next, you will be scheduled for EPR measurements. These should occur approximately one week after the India ink injection and prior to the initiation of your chemotherapy.
- You will report to the Neurology Clinic for all neurologic assessments. Neurologic assessment includes history, standard questionnaires, and sensation testing. These can occur on the same day that you review and sign the consent form, or at a different date prior to the initiation of your chemotherapy.
    - Nerve Conduction Studies (NCS) and Sudoscan
        - NCS measures how quickly electrical signals move through your nerves. This test will help your doctor determine if there is damage to your nerves.
        - During the NCS, small metal disks – called recording electrodes – are taped to the surface your skin on one part of your body. Another pair of electrodes will be attached to the skin of a nearby part of your body. A brief electric shock will be delivered to the surface of your skin and the electrical current will be measured as it moves from the site of stimulation to the recording electrodes.
        - NCS will not harm you, but it may cause some pain.
        - Sudoscan is a device that measures the sweat glands in your hands and feet. This measurement can tell us about the function of the small nerves that are affected in CIPN. The scan takes only a couple of minutes to complete. You will be asked to remove your shoes and socks, and you will stand on two metal plates. You will also rest your hands on two other plates that will be placed at a comfortable height. During the scan, you may feel a subtle tingling sensation or you may feel nothing at all. Sudoscan is approved by the FDA and is safe for use in a clinical setting.
- **Visit 1b: EPR Oximetry Measurement (Approximately 30-45 minutes per EPR oximetry measurement)** All EPR oximetry measurements will be done in a private room in the Radiation Oncology Suite at Dartmouth-Hitchcock Medical Center (DHMC). When you receive EPR oximetry measurements, you will be asked to sit in a chair,

which will be wheeled between the two disks of the EPR magnet. The location of the ink injection will be placed at the center of the magnet.

- The magnet used for measuring oxygen is a low field magnet (about 50 times less powerful than the magnet used for MRI); this magnet is approximately the strength of a very strong refrigerator magnet. The EPR machine uses low-level microwave power (about the same as what a cell phone emits during a single call) to detect the amount of oxygen at the sites where the India ink was injected.
- We would like to see if the amount of oxygen in your tissues changes depending on whether you breathe normal, room air (which is 21% oxygen) or pure (100%) oxygen. Therefore, we will make three consecutive measurements: first while you breathe usual room air, second while breathing 100% oxygen delivered through a hospital gas-delivery mask, and then while breathing room air again. Each measurement will last approximately 10 minutes while you are sitting in a chair, staying still and relaxed and taking normal breaths throughout. This complete procedure should take about 30-45 minutes total.
- We will ask you to complete as many as five measurements prior to beginning your chemotherapy treatment. These measurements may be done during one visit, or spread out over multiple days if you prefer.

Visit 2: Approximately 2-5 hours

- At the mid-point of your chemotherapy treatment, or as soon as you show signs of CIPN, you will be contacted to schedule a second visit. Just like Visit 1a, you will report to the Neurology Clinic at DHMC for clinical and electrophysiological assessments. You will also return to the Department of Radiation Oncology for the second set of up to five (5) EPR measurements. These measurements will be the same as Visit 1b, and will take 30-45 minutes each.

Visit 3: Approximately 2-5 hours

- At the completion of chemotherapy, you will be contacted for a third and final visit. All tests and study procedures at Visit 3 will be the same as Visit 2.

Unscheduled EPR Oximetry Measurements: Approximately 30-45 minutes per EPR oximetry measurement

- If you develop symptoms of CIPN, your symptoms may fluctuate. You may be asked to participate in unscheduled EPR oximetry measurements if you have changes in your CIPN symptoms.

Blood Draws for Neurofilament Light Chain (NF-L) Biomarker: Prior to the start of chemotherapy, prior to each scheduled chemotherapy treatment, and after the completion of chemotherapy, you will be asked to provide a blood sample (1-2 tablespoons) that will be tested for levels of NF-L. All attempts will be made by the study team to obtain the blood sample at the time of your clinical blood draw prior to chemotherapy. If you do not have a scheduled blood draw, you have the option of having blood drawn only for research purposes.

Blood Draw for Genetic Research (Optional): The next time that you have blood drawn as part of your normal care, with your permission, we may ask that an additional tube of blood (1 – 2 tablespoons) be drawn for deposit into the CIPN genetic bank. If you do not have a scheduled blood draw, you have the option of having blood drawn only for research purposes.

What is a genetic bank? A genetic bank, or biobank, is a collection of biological samples donated by patients. Scientists study the genes and other molecules in the specimens to learn more about diseases and to discover new treatments. For this study, we would be looking for unique genetic signatures of people who develop CIPN.

Do I have to participate? **No**. Participating in the biobank is voluntary. Your decision whether or not to take part will have no effect on the quality of your medical care. On the signature page of this consent form, there is an additional box that you can check if you wish to participate in the CIPN genetic bank.

Will I benefit from participating? The long-term goal of the biobank is to better diagnose and treat CIPN, however, you will not personally benefit from donating your blood.

Will I get results from the genetic analysis of my specimens? We do not expect to give you any results from the tests done on your blood sample. The tests that will be done using your blood will be done for research purposes only and will not result in information that is useful to your medical care. However, as we learn more, it is possible that clinically useful information could be learned from the research. We will tell your doctor if that happens.

What are the options if you do not want to take part in this study?

EPR oximetry and testing blood samples for levels of NF-L are not treatments for CIPN; they are being studied as a tool to more effectively diagnose and screen people at high risk for developing CIPN. By participating in this study, you will receive treatment-as-usual for symptoms of CIPN. If you decide not to participate in this study, you will receive the same standard treatment for CIPN. If you do not wish to receive EPR oximetry and give blood samples for testing of NF-L, you cannot take part in this study. Because it is experimental as a measure for CIPN, you can only receive EPR oximetry and have testing for NF-L in a research study.

If you take part in this study, what activities will be done only for research purposes?

EPR oximetry measurements, the India ink injection, the Sudoscan, blood draws for NF-L, and standard questionnaires at all visits will be done only for research purposes.

All other procedures, tests, and activities described in Visit 1 are being done only for research purposes.

If you do not develop symptoms of CIPN, all other procedures, tests, and activities described in Visits 2 and 3 will also be done only for research purposes. However, if you develop

symptoms of CIPN, all other procedures, tests, and activities will be considered standard of care for all visits after you begin developing these symptoms.

What are the risks involved with taking part in this study?

India Ink:

Common

- Mild discomfort from placing the India ink (and a local anesthetic if used) under the skin using a needle and syringe. Mild bleeding from the injection may occur.
- Minor swelling and mild discomfort can occur and persist for up to 3 days.
- The black spot of ink is **permanent** and visible on the surface of the skin.

Sometimes

- There is a small chance of the India ink may spread, resulting in a larger black spot than is expected and greater discomfort.
- Over time, a bump may appear on the surface of the skin over the ink injection. This is a response of the body to a foreign substance and is not serious.

Rare (less than 1-2 times per 100 people)

- There is a small chance of the ink migrating, resulting in an additional spot(s) a short distance from the original location. This is not serious.
- There is a small chance of allergic reactions that may occur within a few minutes and may persist, resulting in some or all of the following symptoms: redness, swelling, inflammation, itching, pain, or rash or sensitivity to being in light. These problems may or may not be serious.
- There is small chance of chronic irritation or discomfort associated with the ink injection. These problems may or may not be serious.

Possible Risk of False Readings on PET/CT Imaging Scans and need for a Biopsy

For some types of malignancies (such as head and neck tumors), oncologists may advise patients to undergo PET/CT imaging to look for possible spread or recurrence of the tumor. ('PET/CT' stands for Positron Emission Tomography/Computed Tomography.) For the PET/CT, the patient is injected with an imaging agent which, if the agent does concentrate in one or more areas, may be a sign of tumor growth. However, concentration of the agent may also show up for other reasons that are unrelated to cancer; in these cases, where the scan finds a concentration that is not related to cancer, the reading is referred to as being a false positive (in other words, is a 'false alarm' about cancer). A false positive about cancer may cause your doctor to order a biopsy, where some tissue is removed and analyzed under a microscope. Because there is some evidence that the ink injection site can sometimes show up as a false alarm on a PET/CT scan, we advise you, if your doctor suggests you have a PET/CT scan, to tell your doctors about your ink injection and that it might show up as a localized region on your PET/CT scan, so your doctors can be aware of this possibility in interpreting your scans and planning any next steps. You and your doctor are welcome to

contact us for more information in the event that you have an apparently positive PET/CT scan in the area of your ink injection.

EPR Oximetry:

- There are no expected risks from breathing pure oxygen for about 10 minutes.
- There are no expected risks from the oxygen measurement itself.

Nerve Conduction Studies

- It is common to experience some pain or discomfort from the electric current used in NCS. Most patients describe this discomfort as mild. This sensation may feel like a quick tingling, a twitching of the muscle, or a brief burning pain. The test can also cause some people to feel anxious. Remember that the electrical current being used is a very low-voltage and each electrical pulse is less than a split-second.

Blood Draw for Neurofilament Light Chain (NF-L) Biomarker:

- There are no health risks associated with donating blood for testing of the biomarker, NF-L, although you may experience some mild and temporary discomfort at the site of injection. This test involves a biomarker in your blood and does not involve analyzing your DNA.

Blood Draw for Genetic Research (Optional):

- There are no health risks associated with donating blood for future testing, although you may experience some mild and temporary discomfort at the site of injection. Genetic research involves studying your DNA, which contains information about you and your family. If this information was released or compromised, there is potential for it to result in certain kinds of discrimination against you or your family. In the United States, the "Genetic Information Non-Discrimination Act" (GINA) is a law that protects you against employers or health insurance companies using your genetic information to make decisions. Because technology is developing very quickly in genetic science, there may be risks in the future that we cannot predict. Additionally, we will do everything that we can to protect your genetic information from being released.

You should report any problems to your doctor or to the director of this study**:** Victoria Lawson, MD.

<u>Other important items you should know:</u>

- Your decision whether or not to participate in this study, or a decision to withdraw will not involve any penalty or loss of benefits to which you are entitled.
- **Product Development:** If the results of this research are used towards the development of a commercially available product, you will not receive any extra compensation.

- **Financial Disclosure:** Dr. Harold Swartz and other researchers working on this study do have a reported financial interest in the EPR technology. A committee at Dartmouth College has evaluated this relationship and has developed a management plan to ensure that objectivity in the research is maintained.
- **New Information**: New information related to this research will be made known to you when it becomes available. This may affect your decision to stay in this study.
- **Withdrawal from the study:** You may choose to stop your participation in this study at any time. Your decision to stop your participation will have no effect on the quality of your medical care.
- A description of this clinical trial will be available on 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.
- **Funding:** This research is funded by The Reeves Fund and Disarm Therapeutics.
- **Number of people in this study:** We expect 30 people to enroll in this study.

How will your privacy be protected?

The information collected as data for this study includes: information about your chemotherapy treatments, neurologic and medical history and clinical assessment results, NCS results, EPR oximetry results, blood samples for testing of NF-L, a blood sample for genetic testing, and the questionnaires. We will also collect information about you such as your name, age, sex, gender, and medical record number.

We are careful to protect the identities of the people in this study. We keep the information for this study – both the paper and electronic data – secure and confidential. Your physical, paper data will be stored in the Clinical Research Office of the Department of Neurology in a locked office. All electronic data will be safely stored with encryption on DHMC servers. Your name will not be used in any published results of this study. Furthermore, once the study is complete, we will use a "limited data set" to analyze all the study data, which will be stripped of identifiers such as your name, medical record number, address and telephone number.

The information collected for this study will be used only for the purposes of research as stated earlier in this form.

Who may use or see your health information?

By signing this form, you allow the research team to use your health information and give it to others involved in the research. The research team includes the study director plus others working on this study at Dartmouth-Hitchcock Medical Center and elsewhere. You also permit any health care provider holding health information needed for this study to give copies of your information to the research team.

The information collected for this study may be used by researchers or officials of the following institutions.

- Dartmouth College
- Mary Hitchcock Memorial Hospital
- Dartmouth-Hitchcock Clinic
- Dartmouth-Hitchcock Medical Center
- The Dartmouth-Hitchcock Health Institutional Review Board (IRB)
- Disarm Therapeutics

Some of the information used in this study, called Protected Health Information ("PHI"), is protected by federal privacy laws. By signing this consent form, you give your permission to have your PHI collected, used and disclosed for purposes of this study. Your permission to use your health information for this study will not end until the study is completed. During this study, you and others who take part in the study may not have access to the study data. You may ask for study data once the study is over. You have a right to receive a copy of the information in your medical record at any time.

It is possible for a court or government official to order the release of study data including information about you.

What if you decide not to give permission to use and share your personal health information?

If you do not allow use of your health information for this study, you may not take part in this study.

If you choose to stop taking part in this study, you may cancel permission for the use of your health information. You should let the researcher know if you want to cancel your permission. The study team will assist you in putting your wishes in writing. Information collected for the study before your permission is cancelled will continue to be used in the research.

Whom should you call about this study?

If you have questions about this study or need to report a study related injury, you can call your doctor or the research director for this study: Dr. Lawson at (603) 650-5104 or Kendra Hebert (Project Coordinator) at 603-650-1951 during normal business hours.

For urgent matters outside the normal business hours, call (603) 650-5000 and request to speak with the "on-call resident neurologist."

If you have questions, concerns, complaints, or suggestions about human research at Dartmouth-Hitchcock Medical Center, you may call the Dartmouth-Hitchcock Health Institutional Review Board (IRB) (603) 650-1846 during normal business hours.

What about the costs of this study?

The medical tattoo (India ink), all blood draws for NF-L and genetic banking, and EPR oximetry will be supplied free of charge by the sponsor in addition to all of the tests/procedures described for Visit 1. Insurance plans are billed only for study procedures that are the usual care for your condition. Some of the medical care that you will receive during this study is the usual care a doctor would recommend for your condition. If you develop signs of CIPN, the neurology clinic visits will be considered usual care. You or your insurance plan will be expected to pay for the costs of this usual medical care.

For assistance in determining your coverage, please call the billing specialist in DHMC Patient Financial Services at 603-653-1047 or 800-368-4783. Please provide the billing specialist with the protocol number, D17062.

Will you be paid to take part in this study?

You will not be paid for taking part in this study.

What happens if you get sick or hurt from taking part in this study?

Sponsor Information: This research is funded by a grant from The Reeves Fund and Disarm Therapeutics. If you develop an illness or have an injury because you are in this research study, the sponsor will not pay for:

- The costs that are covered by your health insurance plan, or
- Treatment of illness or injury that results from the negligence of a health care provider, or
- Treatment of a condition that you had before you were in the study.

The sponsor will not offer any other payments for your study-related illness or injury such as lost wages, expenses other than medical care, or pain and suffering.

Local Information: If you are injured or become ill as a result of research procedures, you will be provided with medical treatment but the following organizations do not plan to pay for this treatment.

- Mary Hitchcock Memorial Hospital
- Dartmouth-Hitchcock Clinic
- Dartmouth-Hitchcock Medical Center
- Trustees of Dartmouth College
- The Department of Neurology and DHMC
- The Reeves Fund
- Disarm Therapeutics

If you have any questions or concerns about the legal responsibility of these organizations, please call the Mary Hitchcock Memorial Hospital Office of Risk Management at (603) 650-1250 during normal business hours. If you agree to take part in this study and you sign this consent form, you are not giving up any of your legal rights.

Your responsibilities as a person taking part in this study

(1) Be aware it is important for your safety that the research team knows about your medical history and current condition.

(2) Notify the research team immediately if you suffer any injury or unexpected reaction to the study procedures.

(3) Seek treatment with the help of the research team if you suffer any injury or unexpected reaction to the study procedures.

(4) Make reasonable efforts to follow the instructions of the research team.

CONSENT

I have read the above information about *Biomarkers in chemotherapy-induced peripheral neurotoxicity: better tools and understanding* and have been given time to ask questions. I agree to take part in this study and I will be given a copy of this signed consent form.

Please check this box and sign your initials if you **DO WISH** to participate in the CIPN genetic bank: ☐ (initials) _____

Participant's Signature	Date & Time	PRINTED NAME

Researcher or Designee Signature	Date & Time	PRINTED NAME