Official Title: A Phase II Trial of Nifurtimox for Refractory or Relapsed Neuroblastoma or Medulloblastoma.
NCT00601003
IRB-Approved Date: 1/19/16

Helen DeVos children's hospital
a member of SPECTRUM HEALTH

Patient name
DOB
MRN
Physician
FIN

Permission to Take Part in a Human Research Study & HIPAA Authorization for Release of Health Information for Research Purposes

Title of research study: A Phase II Trial of Nifurtimox for Refractory or Relapsed Neuroblastoma or Medulloblastoma

Sponsor: The Neuroblastoma and Medulloblastoma Translational Research Consortium (NMTRC)

Investigator: Deanna Mitchell, MD

"You" refers to you, or you and your child

"We" refers to Helen DeVos Children's Hospital

You are being asked to volunteer in this research study because you have recurrent or unresponsive neuroblastoma or recurrent medulloblastoma that cannot be cured by any other known treatment.

What you should know about a research study?

- Someone will explain this research study to you.
- You volunteer to be in a research study.
- Whether or not you take part is up to you.
- You can choose not to take part in the research study.
- You can agree to take part now and later change your mind.
- Whatever you decide it will not be held against you.
- Feel free to ask all the questions you want before you decide.

Who can I talk to?

If you have questions, concerns, or complaints, or think the research has hurt you talk to the investigator or members of the research team at [redacted].

This research has been reviewed and approved by the Spectrum Health Institutional Review Board. You may talk to them at [redacted] or [redacted] for any of the following:

- Your questions, concerns, or complaints are not being answered by the investigator or research team.
- You cannot reach the investigator or research team.
- You want to talk to someone besides the investigator or research team.
- You have questions about your rights as a research participant.
- You want to get information or provide input about this research.

Why are we doing this research?

This study is being done to test the effect of a drug, Nifurtimox, against neuroblastoma and medulloblastoma in children. Nifurtimox is a drug that has been used in South America for many years to treat a parasitic disease known as Chagas Disease. Nifurtimox is not approved by the Food and Drug Administration for routine use in treating neuroblastoma or medulloblastoma in the United States, but early observations suggest that Nifurtimox may have anti-tumor properties. To participate in this study, you must be 0 to 21 years old, have adequate liver function, and have recurrent neuroblastoma or medulloblastoma.

From clinical experience in South America, we know that children can tolerate Nifurtimox when given by mouth, and it appears to have no long-term side effects when used to treat Chagas Disease. Based on laboratory and animal studies, we believe that drug levels similar to those used to treat Chagas Disease may shrink/kill neuroblastoma cells, especially when combined with other chemotherapy drugs.

The purpose of this study is to see whether Nifurtimox, when taken in combination with other chemotherapy drugs, will shrink/kill neuroblastoma or medulloblastoma cells. The study will also look at the side effects when taken in this manner.

The chemotherapy drugs that have been recommended for this study are approved by the US Food and Drug Administration (FDA) and have been used in the past to treat patients with neuroblastoma and medulloblastoma. These chemotherapy drugs are cyclophosphamide, topotecan, and zoledronic acid.

How long will I be in the research?

We expect that you will be in this research study for about 18 months. You will have 6 months of treatment and then your disease status will be monitored at set intervals for an additional 12 months after your treatment is done.

If you respond well to the study treatment, your study doctor may decide to keep you on Nifurtimox for longer than 6 cycles. The number of additional cycles will be determined by your doctor. If you stay on Nifurtimox, you will be in the study for longer than 18 months, and your disease status will be monitored for 12 months following the last dose.

How many people will be studied?

It is anticipated that approximately 100 patients will participate between multiple study sites. We expect to enroll four to six patients a year at Helen DeVos Children's Hospital.

What happens if I say yes, I want to be in this research?

If you agree to be in the study, and the exams, tests and procedures show that you can be in the study, your study treatment will take place in the outpatient clinic according to the following schedule:

You will participate in six individual cycles of therapy. During these cycles you will take Nifurtimox three times per day by mouth every day of the study. You will also receive intravenous (IV) cyclophosphamide and topotecan. Cyclophosphamide and topotecan will be given through your vein with an IV or through your central line. Each drug will be given over 30-60 minutes, for 5 days in a row at the beginning of each 21 day cycle. Study visits will occur as described below, and all required tests are described in detail later in this section of the consent form.

You must be seen at your study institution clinic during the entire Week 1 of Cycle 1. All required radiology scans (MIBG's and MRI/CT's), must be done at the study institution unless otherwise approved by the Sponsor. If Helen DeVos Children's Hospital is not your home institution, all other care (except for the study procedures described below) can be done at your home institution at the discretion of your study doctor.

Treatment Description

Before study entry:

After consent form is signed, certain tests and assessments must be completed before you can start study treatment. If you have had any of these tests recently, you may not need to have them done again. Your study doctor will tell you if any tests need to be repeated.

The following tests must be done within 30 days of starting study treatment:

- CT or MRI of measurable disease sites
- MIBG scan (if you have had an avid/ positive scan before. MIBG not required for patients with medulloblastoma.)
- Bone Marrow Aspirate and Biopsy (required for neuroblastoma subjects, may not be necessary for medulloblastoma subjects)
- Lumbar Puncture for cerebral spinal fluid (CSF) collection and testing (medulloblastoma subjects only)

The following tests must be done within 7 days of starting study treatment:

- Complete physical exam, including neurological exam and a Clinical Total Neuropathy Scale (TNSc)
- Urine catecholamines (neuroblastoma subjects only)
- Urine pregnancy test for all female subjects age 13 and older
- Labs: CBC with differential, electrolytes, kidney function tests (BUN and creatinine), and liver function tests (LDH, AST, ALT, Ferritin)
- Neurologic structured interview and questionnaires
- Additional imaging or studies may be done if your doctor thinks they are needed

Cycle 1:

You will be closely monitored during the first cycle. Each cycle requires you to visit the clinic 5 days in a row to get your IV chemotherapy, but the first cycle is a bit different. We are not sure how long your study visits will take. There are special blood draws done on Day 1 and

Day 4 that might require you to stay longer than usual, and there are two additional visits required during the first cycle. Cycle 1 visits include:

- Day 1
  - IV Chemotherapy (all IV chemotherapy will be given in clinic)
  - Nifurtimox pill count
  - Blood draw before first dose of Nifurtimox
  - Blood draw 3 hours after first dose of Nifurtimox
- Day 2
  - IV Chemotherapy
- Day 3
  - IV Chemotherapy
- Day 4
  - IV Chemotherapy
  - Blood draw before first dose of Nifurtimox
  - Blood draw 3 hours after first dose of Nifurtimox
- Day 5
  - IV Chemotherapy
- Day 8 (+/- 3 day visit window)
  - Physical exam, including neurological exam
  - Labs: as described in the "Before Study Entry" section above
- Day 15 (+/- 3 day visit window)
  - Same as Day 8 visit
- Days 1-21
  - Nifurtimox will be taken by mouth 3 times a day, as directed

Before each of the remaining cycles (2-6) the following tests need to be completed:

- Physical exam, including neurological exam
- Labs as previously described
- Urine Catecholamines (neuroblastoma subjects only)

Cycles 2 and 4:

- Day 1: Pill count and drug diary collection
- Days 1-5
  - IV Chemotherapy
- Days 1-21
  - Nifurtimox will be taken by mouth 3 times a day, as directed
- Before next cycle starts:
  - CT or MRI of disease sites
  - MIBG (previously avid/positive neuroblastoma subjects only)
  - Lumbar Puncture for CSF collection and testing (medulloblastoma subjects only, and only if positive at study entry)
  - Neurologic structured interview, TNSc, and two questionnaires
  - Additional imaging or studies may be done if your doctor thinks they are needed

Cycles 3, 5 and 6:

- Day 1: Pill count and drug diary collection
- Days 1-5

    - IV Chemotherapy
- Days 1-21
    - Nifurtimox will be taken by mouth 3 times a day, as directed

During each cycle after your 5 days of IV chemotherapy are done, you may start subcutaneous injections (shot under the skin) of filgrastim or pegfilgrastim to help your body make white blood cells if your body can't make them on its own.

To keep track of missed Nifurtimox doses, you will be asked to fill out a drug diary at home for each cycle of treatment. The diary asks you to check off each dose you take, and make note of any missed doses (including the reason why the dose was missed). Diary pages will be collected at the end of each cycle.

You may have leftover Nifurtimox pills at the end of each cycle. You will be asked to bring any leftover Nifurtimox to your appointment at the end of each cycle.

End of Study Treatment (completion of cycle 6) or Early Withdrawal:

- Remaining supply of Nifurtimox must be turned in
- Pill count and drug diary collection
- Physical and neurological exam and TNSc
- Labs as previously described
- Urine catecholamines (neuroblastoma subjects only)
- Neurologic structured interview and two questionnaires
- CT or MRI re-evaluation of disease sites
- MIBG (previously avid/positive neuroblastoma subjects only)
- Bone Marrow biopsy and aspirate (if positive at study entry)
- Lumbar Puncture for CSF collection and testing (medulloblastoma subjects only, and only if positive at study entry)

If you withdraw from the study early, CT/MRI and/or MIBG scans don't need to be repeated unless your doctor thinks they are necessary.

After your last dose of Nifurtimox:

You will come to the clinic for a follow-up visit 30-37 days after your last dose of Nifurtimox. The following procedures will be done at this visit:

- Physical exam, including a neurological exam
- Neurologic Structured Interview
- Labs as described in the "Before Study Entry" section
- Urine catecholamines (neuroblastoma subjects)

In addition, we will collect information about the status of your disease periodically for a year after your last dose of Nifurtimox. We will either meet with you during routine follow-up appointments or we will contact you by phone at the following intervals:

- 2 months
- 3 months
- 5 months
- 7 months
- 9 months

- 1 year

Continuation on Nifurtimox:
If you respond well to the treatment and you complete all 6 cycles, your doctor may recommend that you continue taking Nifurtimox, either by itself or in combination with other drugs (which may or may not include cyclophosphamide and topotecan). Your doctor will decide how many extra cycles you will need.

The following tests and exams are required within 7 days of starting each cycle:
- Physical exam, including a neurological exam
- Labs as described in the "Before Study Entry" section
- Urine catecholamines (neuroblastoma patients)
- Additional imaging or studies may be done if your doctor thinks they are needed

The following tests and exams are required every three cycles (or sooner, if needed):
- CT or MRI re-evaluation of disease sites
- MIBG (previously avid/positive neuroblastoma subjects only)
- Bone Marrow biopsy and aspirate (if positive at study entry)
- Lumbar Puncture for CSF collection and testing (medulloblastoma subjects only, and only if positive at study entry)

Tests/Evaluations:
If you decide to be in this study, you will have various tests and evaluations performed throughout your study treatment. These tests and evaluations will help monitor your disease, progress, and potential side effects. Most of these exams, tests and procedures are part of regular cancer care and may be done even if you do not join this study. If you have had some of them recently, they may not need to be repeated. Additional tests, procedures, or evaluations may also be included in your care, as determined by your physician.

Optional Biologic Studies:
Along with this study, we are doing additional neuroblastoma and medulloblastoma research using extra blood and bone marrow collected during the screening phase. Extra bone marrow samples will be collected during your routine bone marrow procedures while you are in the treatment phase, and extra blood will be collected periodically at the time of routine blood draws.

If you have a procedure to remove a portion of your tumor while you are in the study, a leftover sample will be sent for optional testing if you choose to take part. If you have archived tumor samples available from a previous surgery, we may also send a part of the tissue if you opt to take part. *You will not be asked to undergo a surgical procedure of any kind to obtain a piece of tumor for the purposes of the optional biologic studies.*

We are also asking all participants for permission to store any leftover specimens in a laboratory for use in future cancer and/or Nifurtimox research. Your participation in the additional biologic studies and the leftover specimen storage are optional. More information about the biologic studies can be found in the "Optional Biologic Studies Consent" section of this form.

Blood samples will be taken from you throughout your treatment to evaluate your progress and measure blood counts. If you already have a central line, blood will be taken from your central line. Otherwise, blood will be drawn from your vein. The amount of blood drawn will vary based upon the test/s performed. Problems associated with drawing blood from a central line include infections and clotting. If blood is taken from your vein, you may experience discomfort, pain, swelling and/or bruising. Sometimes bleeding can occur at the place where blood is drawn. Fainting and infection can also occur, but they are rare.

You will be asked to also have extra research-related blood tests done called pharmacokinetic studies. The pharmacokinetic studies will involve having additional blood samples drawn at specific intervals. Approximately ½ teaspoon of blood would be collected at each interval. These blood samples will be tested in a laboratory to determine the level of Nifurtimox in the blood. This information will be used to better understand the metabolism (break down) of Nifurtimox. This information along with any information about side effects will be used to determine what doses are most effective when using Nifurtimox. The blood samples for the pharmacokinetics studies will be drawn right before taking the morning dose of Nifurtimox and then at 3 hours following the morning dosing on the first and fourth day of treatment during the first and third cycles only. Whenever possible, these tests will be obtained from a central venous line. You will not have to pay for these pharmacokinetic studies.

If you agree to participate in the optional biologic studies, about 1 teaspoon of extra blood will be collected when you have routine blood draws at the following intervals:

- Screening visit
- Cycles 2 and 4
- End of study visit
- Follow-up visits

Urine collections will be needed to measure certain substances that your body gets rid of in the urine. These may be 12 to 24 hour urine collections. Infants and children who are not toilet-trained must have a urinary catheter (flexible sterile rubber tube passed into the bladder) in place 12-24 hours to collect a urine sample. The most common risk of catheter placement is infection. Rarely, injury can occur to the urethra (the tube that leads to the bladder).

Bone Marrow tests (bone marrow aspirations and/or biopsies) are performed to check for some tumors. This is done to evaluate the degree of disease present in the bone marrow. These tests involve removing a sample of bone marrow from the center of a bone. Bone marrow is the place where blood cells are made. A bone marrow test is a procedure that takes only a few minutes. This test is often performed while the child is sedated (made sleepy) to minimize any fear or discomfort. A bone marrow test is usually done in a treatment room with the child lying flat on a table. For a bone marrow aspiration, a medicine is injected into the skin over the hip bone to make it feel numb, and a small, sharp needle is inserted into the bone to remove 1 to 2 teaspoons of bone marrow (which looks like blood). For a bone marrow biopsy, another special needle is used to remove a tiny piece of bone. After the needle is removed, a small bandage is applied. At this time, you may experience intense pressure with brief periods of pain. Pain following the procedure is mild and should resolve within a few days. One risk of this procedure is the remote possibility of infection.

Bruising is possible with some tenderness at the needle insertion site. You will be asked to sign a separate consent form for this procedure.

If you have your bone marrow tested during your study treatment, we will collect extra marrow (between 1-3 teaspoons) for special research testing of neuroblastoma cells, if they are present. Collecting extra bone marrow for the special research is optional. The optional study is described on the "Additional Optional Tumor Biology Consent" page of this consent form. You will be asked to sign the page if you wish to participate in the optional part of the study.

Magnetic Resonance Imaging scans (MRI scans) and/or Computed Axial Tomography (CT scan) will also be performed to evaluate your disease. An MRI is a scan using sound waves that produces very detailed pictures of parts of the body, such as the brain and spinal cord. A CT scan is the process of using computers to make a three-dimensional image from flat x-ray pictures, one slice at a time. The scans will show the doctors where a tumor is and how much is present. A special IV dye (a solution that allows the specific body part studied to show up better when scanned) must be given for some MRI scans. For many young children, sedation medicine (medicine to make you sleepy) must be given for scans that take a long time, because they must hold very still to get clear pictures. Your doctor will explain these radiology tests in greater detail. The test itself is not painful; though there may be some discomfort from the need to remain still. If IV dye is used, it can cause a reaction to people who are allergic, and may increase kidney dysfunction in people with kidney problems. You will be asked to sign a separate consent form for this procedure if sedation is needed.

A lumbar puncture, sometimes called an LP or spinal tap, is a test done to get samples of spinal fluid (the clear liquid that surrounds the brain and spinal cord). The spinal fluid is checked for cancer cells. A lumbar puncture is a procedure that takes only a few minutes. This test is often performed while the child is sedated (made sleepy) to minimize any fear or discomfort. It is usually done in a treatment room with the child lying in a curled position on his/her side on a table. After a small area of skin over the lower back is cleaned and injected with a tiny amount of medicine to make it feel numb, a small, sharp needle is inserted in the lower back to remove about 1-3 teaspoons of spinal fluid. After the needle is removed, a small bandage is applied. There is possibility of local pain at the needle insertion site. There is a small risk of bleeding, headache and very rarely, infection. The chance of permanent neurological (brain, spinal cord, and nerve) damage is extremely low. You will be asked to sign a separate consent form for this procedure.

Nuclear medicine scans (MIBG scan) are tests that use a tiny amount of radioactive tracer given IV to get pictures of certain body parts, such as bones (a bone scan) or the lymph nodes (a gallium scan). The tracer is usually given a few hours before the pictures are taken. You must lie still, so some form of sedation (medicine to make you sleepy) may be needed. Allergic reactions to the radioactive tracer are rare. The level of radiation exposure with these procedures is low. You may be asked to sign a separate consent form for this procedure.

A Clinical Total Neuropathy Scale (TNSc) will be done periodically to check for any changes in your reflexes, strength, movements and how sensitive you are to touch. The neurological exam tells us how Nifurtimox might be affecting these things.

Neurological structured interviews will be performed. Your doctor will ask you to rate any neurological symptoms (such as headache, light sensitivity, upset stomach). The purpose of

the interview is to find out if you are having any side effects that may be related to taking Nifurtimox, and how serious the side effects might be.

Questionnaires will be given to you at study visits for you to complete. There are three different questionnaires that will be used to tell us what your Quality of Life (QoL) is like:

- BRIEF (Behavior Rating Inventory of Executive Function) assessment:
  - This survey helps us get information about the way you behave and think
  - There are 86 statements describing different behaviors. Your parent will be asked to answer whether each behavior is **N**ever (a problem), **S**ometimes a problem, or **A**lways a problem
- PCSQoL:MTD (Pediatric Cancer Survey: For Parents Making Treatment Decisions:
  - This survey will ask your parent to answer questions about how important quality of life is when making treatment decisions
- PCSQoL:DT (Pediatric Cancer Survey: Parent Assessment of Children's Quality of Life During Treatment):
  - This survey will ask your parent to answer questions about how your quality of life changes during treatment.

If you wish to take part in this study, we expect that you will:

- Keep your study appointments. If you cannot keep an appointment, contact your study doctor or research study staff to reschedule as soon as you know that you will miss the appointment.
- Tell your study doctor or research staff about any medications you are taking.
- Fill out your drug diary pages and turn them in at the end of each cycle or the beginning of the next cycle.
- Tell your study doctor or research study staff about any side effects, doctor visits, or hospitalization that you may have whether or not you think they are related to the study therapy.

What happens if I say no, I do not want to be in this research?

You may decide not to take part in the research and it will not be held against you. A refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled.

Instead of being in this research study, your choices may include: Enrollment in another clinical trial that you may qualify for, standard chemotherapy treatment, or radiation. An additional alternative is to accept no further therapy, with palliative care to help you feel more comfortable, an option that would probably result in continued progression of the disease. Please discuss these options with your regular doctor as well as other trusted personal and family advisors. Your treating physician will discuss any potential risks or complications associated with alternative treatments with you.

<u>Important risks and possible benefits of these alternatives</u>:
Because there are no known curative choices for relapsed neuroblastoma and medulloblastoma, alternative therapies could possibly lead to more or less side effects, and may decrease your chance of being cured. The risk of no further therapy is that your HRM will get worse, and the benefit to choosing no further therapy will be receiving fewer interventions. Your treating physician will discuss the comparative risks and benefits for the treatments available for your type of HRM.

What happens if I say yes, but I change my mind later?

You can agree to take part in the research now and stop at any time it will not be held against you.
Discontinuing participation will not result in penalty or loss of benefits to which you are otherwise entitled.

If you decide to leave the research, contact your study doctor immediately so you can talk about alternative treatment options. You will be asked to come back to the clinic 30-37 days after your last dose of Nifurtimox for a follow-up visit. The reason for this visit is to make sure you are safe, and to make sure you are not having any problems from stopping the Nifurtimox. The following procedures will be done at this visit:

- Physical exam, including a neurological exam
- Neurologic Structured Interview
- Labs as described in the "Before Study Entry" section
- Urine catecholamines (neuroblastoma subjects)

In addition, we will collect information about the status of your disease periodically for a year after your last dose of Nifurtimox. We will either meet with you during routine follow-up appointments or we will contact you by phone at the following intervals:

- 2 months
- 3 months
- 5 months
- 7 months
- 9 months
- 1 year

If you stop being in the research, already collected data may not be removed from the study database. You will be asked whether the investigator can continue to collect data from your routine medical care. If you agree, this data will be handled the same as research data.

Could being in this study be bad for me?

There may be some risks in this research study that we do not know at this time. If we learn things, such as new findings, that we think might affect your desire to continue to participate in this study, we will tell you. If major risks are discovered after the study is finished, the sponsor may attempt to contact you.

There might be other side effects that we do not know about yet because Nifurtimox has not been widely used to treat tumors in children. These side effects could be dangerous or life threatening. Side effects of Nifurtimox usually get better if the treatment is stopped, but there is the potential that side effects may persist even after stopping the drug. With drugs like cyclophosphamide and topotecan, there is the risk of death due to side effects. You should talk to your study doctor about any side effects that you have while taking part in the study.

The possible side effects of the study treatment are listed in the following tables:

Risks and side effects related to Nifurtimox:

	Common	Occasional	Rare
	Seen in 21-100 kids out of 100	Seen in 5-20 kids out of 100	Seen in less than 5 kids out of 100
While taking Nifurtimox: .	Gastrointestinal disturbances, such as anorexia with weight loss (loss of appetite), epigastric pain (abdominal or stomach pain), nausea and/or vomiting occur in 20-80% of patients.	Skin rash, headache or vertigo (dizziness)	Central nervous system toxicity including disorientation (confusion), disturbances of equilibrium such as ataxia (clumsiness or unsteadiness), and nystagmus (uncontrolled back-and-forth and/or rolling eye movements); excitation, forgetfulness, insomnia (trouble sleeping), irritability, psychosis (mood or mental changes), seizures (convulsions), muscle weakness, peripheral neuropathy (numbness, tingling, pain, or weakness in hands or feet) and tremors; a high eosinophil count (a kind of white blood cell), fever, impotence (decreased sexual drive or ability), or a low white blood cell count with a risk of infection can occur with high doses
Late: Any time after end of treatment	There are no known late side effects of nifurtimox at this time.		

Risks and side effects related to Cyclophosphamide:

Likely	Less Likely	Rare But Serious

• Loss of appetite
• Nausea
• Vomiting
• Fewer white blood cells in the blood.
  ○ A low number of white blood cells may make it easier to get infections.
• Hair loss
• Decreased ability of the body to fight infection
• Absence or decrease in the number of sperm which may be temporary or permanent which may decrease the ability to have children
	• Abnormal hormone function which may lower the level of salt in the blood
	• Abdominal pain
	• Diarrhea
	• Fewer red blood cells and platelets in the blood
	  ○ A low number of red blood cells may make you feel tired and weak.
	  ○ A low number of platelets may cause you to bruise and bleed more easily.
	• Bleeding and inflammation of the urinary bladder
	• Absence or decrease monthly periods which may be temporary or permanent and which may decrease the ability to have children
		• Heart muscle damage which may occur with very high doses and which may be fatal
		• Abnormal heart rhythms
		• Damage and scarring of lung tissue which may make you short of breath
		• A new cancer or leukemia resulting from this treatment.
		• Damage or scarring of urinary bladder tissue
		• Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure, rapid heart rate chills and fever
		• Infertility which is the inability to have children

Risks and side effects related to Filgrastim (G-CSF) or Pegfilgastim include:

Likely	Less Likely	Rare but serious
Aching or pain in the bones	• Pain, redness, itching, and hardening of the skin and bruising at the site of the injection • Headache • Higher than normal levels of liver enzymes in the blood which may indicate liver irritation or damage • Increase of uric acid in the blood • A low number of platelets in the blood which may cause you to bruise and bleed more easily • Low fever • Enlargement of the spleen (an organ in the abdomen/belly which stores blood cells) which may cause pain in the abdomen or left shoulder • Higher than normal white blood count • Skin condition marked by fever and painful skin lesions that appear mainly on the face, neck, back and arms • Rash or worsening of rash[1] • Inflammation of blood vessels in the skin leading to a raised purple rash and bruising has been seen mainly in patient who are treated for a long time[1] Overall reddening with feelings of warmth[2]	• Allergic reactions which can be life threatening with shortness of breath, low blood pressure, rapid heart rate, hives, itching, and facial swelling. • Serious allergic reaction which can be life threatening with rapid build-up of fluid under the skin, in the lining of the intestine, and possibly in the throat or swelling of the tongue which could make it difficult to breath[2] • If you are known to have sickle cell disease, filgrastim or pegfilgrastim may cause a sickle cell crisis. • Severe damage to the spleen (an organ in the abdomen/belly which stores blood cells) which could lead to pain and loss of blood into the abdomen (belly) and maybe life threatening • Difficulty breathing and lung damage that may be due to the white blood cells that are stimulated by filgrastim or pegfilgrastim traveling to the lungs when they are inflamed or infected. • A blood disorder or leukemia that has only been seen in patients with certain immune disorders who are treated for a very long time[1]

[1] Reported with filgrastim [2] Reported with pegfilgrastim

Risks and side effects related to Topotecan:

Likely	Less Likely	Rare But Serious

• Diarrhea
• Nausea
• Vomiting
• Constipation
• Fewer white blood cells, red blood cells and platelets in the blood.
  ○ A low number of white blood cells can make it easier to get infections
  ○ A low number of red blood cells can make you feel tired and weak
  ○ A low number of platelets causes you to bruise and bleed more easily
• Fever including fever with a low white blood cell count which could indicate infection and may require hospitalization and treatment with antibiotics
• Pain which may be in your abdomen, back or bones
• A feeling of weakness and/or tiredness
• Temporary hair loss
	• Loss of appetite
	• Elevation in the blood of certain enzymes or bilirubin found in the liver which could indicate liver irritation or damage
	• Headache
	• Rash, hives, itching or a red bumpy rash
	• A mild lowering of the blood pressure which usually does not require treatment
	• Inflammation and/or sores in the mouth, throat and/or esophagus
	• An infection in the blood which will require admission to the hospital and treatment with antibiotics
	• Numbness and tingling in the fingers and toes
	• Small amount of blood and/or protein in the urine or an elevation in blood creatinine which may indicate mild kidney damage
	• Shortness of breath
	• Muscle or joint aches and pains
	• Chest pain
	• Shaking chills
		• Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure and a rapid heart rate
		• Severe allergic reaction which can be life threatening with rapid build-up of fluid under the skin, in the lining of the intestine and possibly in the throat or swelling of the tongue which could make it difficult to breath.
		• Bleeding into the tumor which may cause damage depending on the location of the tumor

Possible Drug Interactions with Nifurtimox

Propofol is a drug that is used for sedation (anesthesia). You may receive propofol if you have surgery, or a procedure that requires you be sedated such as a bone marrow aspiration, CT Scan, or MRI scan.

In a previous study using Nifurtimox in this population, there have been some possible incidences of what seems to be an interaction between Nifurtimox and extended use of propofol (greater than 1 hour). We are currently recommending that for any procedure that will use propofol for greater than 1 hour, the study drug (Nifurtimox) be held for 24 hours prior to the procedure. If the Nifurtimox cannot be held for 24 hours prior to a procedure that might use extended length (greater than 1 hour) of propofol, we would request an alternative medicine be used for sedation. This will be at your treating physician's discretion. We have not seen any incidences of increased side effects with short duration use of propofol (less than 1 hour) at this time.

Although the risk of seizures using Nifurtimox alone, in otherwise healthy people, at the 20mg/kg dose level is rare (less than 5 in 100 people), in the Phase I study, we noticed an increased risk of seizures as the Nifurtimox dose level increased. We observed a 1 in 3 chance of a seizure while on the higher dose level (40mg/kg/day of Nifurtimox) in our study patients.

If you have a history of seizures, it is recommended that you start on an anti-seizure medication prior to starting this study. You can discuss this with the study doctor during screening. If you experience a seizure while on study, we ask that you contact your physician immediately. You will then receive an MRI to try to determine if there is a specific cause, other than the Nifurtimox, for the seizure. We would then most likely start you on an anti seizure medication, as long as you continue on the Nifurtimox, to prevent any further seizures.

Under Michigan law, an HIV and hepatitis test may be done on you (or your child) without your consent if a healthcare worker is exposed to your (or your child's) blood or other bodily fluids. If the results of an HIV or hepatitis test indicate that you (or your child) are HIV or hepatitis positive, you will be told about these results and given information about the disease, treatment resources, and other options.

Possible Drug Interactions between Nifurtimox and Metronidazole

Metronidazole is a drug that is used to treat diarrhea caused by infection with Clostridium difficile, a spore-forming bacterium.

During the course of this study there have been two incidences of severe neurotoxicity that may have been possibly related to an interaction between metronidazole and nifurtimox. Although it has not been absolutely determined that it was this combination of drugs that caused the symptoms, due to the possibility that it was the combination, we are requesting that these two drugs not be used together. Please discuss any planned metronidazole use with your study doctor.

Pregnancy/Birth Control:

If you are or become pregnant during this study, there may be additional risks to you, or to your baby. Some of these risks may be known, but some risks may not be known and may not be foreseeable. Because the risks to embryo/fetus/unborn babies and babies who are breast feeding may not be known or foreseeable, pregnant women and nursing mothers are not allowed to join this study. If you are a woman who can get pregnant, you should not become pregnant during this study.

Both male and female study subjects, of child-bearing age, need to agree to use one of the more effective birth control methods during treatment and for six months after treatment is stopped. These methods include total abstinence (no sex), oral contraceptives ("the pill"), an intrauterine device (IUD), levonorgestrol implants (Norplant), or medroxyprogesterone acetate injections (Depo-provera shots). If one of these cannot be used, contraceptive foam with a condom is recommended.

If you think you are pregnant or if you become pregnant during the study, you must tell the study doctor right away. It is important to tell your doctor because there may be risks to you or your baby if you continue in the study.

Women who can get pregnant must have a negative urine pregnancy test before being allowed to join in this study.

In addition to these risks, this research may hurt you in ways that are unknown. If we learn of new risks that we think might affect your desire to stay in the research we will tell you. It is possible, if major risks are discovered after the study is finished, the sponsor may attempt to contact you.

Will I need to pay for any of the tests or procedures in the study?

Taking part in this research study may lead to added costs to you. You or your health insurance company will be responsible for the costs of all standard medical care (including physician visits, tests, procedures, evaluations) and/or hospitalizations. You or your health insurance will be billed for this procedure. If your insurance company requires any co-payment or deductible, you will be responsible for making that payment.
While you are a participant in this study, Nifurtimox will be provided at no cost by Bayer Pharmaceuticals, the manufacturer of Nifurtimox. You will not have to pay for the pharmacokinetic studies, or the blood tests monitoring the blood level of Nifurtimox.

Will being in this study help me in any way?

It is possible that treatment with the study medication may result in improvement of your disease; however, this has not yet been proven. You may not benefit from your participation in this study. The information we learn in this study may help us to better understand your disease or illness and may help develop new ways to diagnose and treat it.

What happens to the information you collect?

Efforts will be made to limit your personal information, including research study and medical records, to people who have a need to review this information. We cannot promise complete confidentiality. Organizations that may inspect and copy your information for quality assurance and data analysis include:

- The Investigator and his/her research staff
- Spectrum Health and its affiliates
- The Spectrum Health Institutional Review Board (IRB) and staff
- Representatives from the Food and Drug Administration (FDA) or other governmental regulatory agencies
- Bayer Pharmaceuticals (the manufacturer of Nifurtimox),
- Representatives from Helen DeVos Children's Hospital-Spectrum Health,
- Representatives from the Neuroblastoma and Medulloblastoma Translational Research Consortium (NMTRC) and its affiliates.
- Your primary care provider

Some of these organizations may be given direct access to your medical records for verification of the research procedures/date involved. By signing this document you are authorizing this access.

The information collected for this study that is sent to the sponsor is the property of the sponsor, and you will not be able to get it back. Your information is protected by keeping your information in a safe place, limiting the people who have access to your information, and limiting how the information may be used. Each subject will be given a unique identifier number. This unique identifier will be kept on a "Subject Identification Log" at each site. Details about permitted uses and disclosures of your information are described under the HIPAA Authorization section of this document. We may publish the results of this research. However, we will keep your name and other identifying information confidential.

Federal law provides additional protections of your personal information. These are described in a later section.

Can I be removed from the research without my OK?

The person in charge of the research study or the sponsor can remove you from the research study without your approval. Possible reasons for removal include if he or she believes it is in your best interest, if you do not follow the study requirements, or if the study is stopped.

If you are removed from the study without your OK, you will be asked to come back to the clinic 30 days after your last dose of Nifurtimox for a follow-up visit. The reason for the visit is to make sure you are safe and that you are not having any problems from stopping the Nifurtimox. The following procedures will be done at this visit:

- Physical exam, including a neurological exam
- Neurologic Structured Interview
- Labs as described in the "Before Study Entry" section
- Urine catecholamines (neuroblastoma patients)

We will contact your treating physician periodically for a year after your last dose of Nifurtimox to collect data on your disease status.

What if I'm injured or made sick from the research?

If you are injured or made sick from taking part in this research study, medical care will be provided. No funds have been set aside to pay you in the event of a research related injury. Contact the investigator for more information. By signing this consent form you will not be waiving any of your legal rights which you otherwise would have if you were not participating in a research study.

What else do I need to know?

You will not be paid for participating in this study.

This study is or will be listed in an online registry. U.S. law requires this. A registry is a place where information is collected. You can see this registry at the website www.ClinicalTrials.gov. The U.S. government runs this website. You and anyone else can visit this website at anytime. You can get information about this study and other studies on this website. Your personal information will NOT be shown on the website.

Dr. Giselle Sholler, a sub-Investigator at Helen DeVos Children's Hospital, serves as the Chair of the Neuroblastoma and Medulloblastoma Translational Research Consortium (the sponsor of this trial), and may benefit financially based on the trial outcome. Therefore, Dr. Sholler has agreed to not take part in patient enrollment and informed consent for this trial. Should you have any concerns or questions regarding this statement please feel free to speak further with the research team or you may call the Spectrum Health Institutional Review Board at [redacted].

HIPAA Authorization for Release of Health Information for Research Purposes

The information we are asking to use and share is called "Protected Health Information." It is protected by a federal law called the Privacy Rule of the Health Insurance Portability and Accountability Act (HIPAA). In general, we cannot use or share your health information for research without your permission.

What will be done with my information?

This information will be collected and entered in a database along with the information from other people taking part in this study.

Why am I being asked to release it?

Your health information will be used to determine if Nifurtimox, either alone or in combination with other chemotherapy drugs, will shrink neuroblastoma or Medulloblastoma cells.

What will be released?

To complete this research study, we will need to collect and release (disclose) information about you.
This information may include:

- Your date of birth, name, contact information, medical record number, and insurance information.
- Existing and ongoing medical records and medical history.
- New health information collected for purposes of this study.

Who will use it or share it?

- The investigator and his/her research staff
- Spectrum Health and its affiliates
- The Spectrum Health Institutional Review Board (IRB) and its staff
- The Food and Drug Administration (FDA)
- The Sponsor of the research: Neuroblastoma and Medulloblastoma Translational Research Consortium (NMTRC) and its affiliates
- Bayer Pharmaceuticals (the manufacturer of Nifurtimox)
- Other collaborating institutions
- Agencies that accredit the hospital or the research program

Once your protected health information has been disclosed it is possible that anyone who receives that information may re-disclose it. Because some of these individuals who receive your protected health information may not be required by law to keep your information confidential, we cannot guarantee that your information will not be released or made

available to another party once it leaves Spectrum Health. Therefore, we share your information only if necessary and we use all reasonable efforts to request that those individuals who receive your information take steps to protect your privacy.

How long will my health information be used?
This authorization has no expiration date.

Can I stop my protected health information from being used?
You can tell us to stop using and sharing health information that can be traced to you at any time. We will stop, except in very limited cases if needed to comply with law, protect your safety, or make sure the research was done properly. If you have any questions about this please ask. If you want us to stop, you must tell us in writing. Write Dr. Deanna Mitchell at the following address:

Deanna Mitchell, MD
[redacted]

What happens if I do not want you to collect and release my information?
If you decide not to authorize release of your health information as part of this study, your decision will in no way affect your medical care or cause you to lose any benefits to which you are entitled. You cannot participate in this research study if you do not authorize the use or release of your PHI.

When will it be destroyed?
We do not know when your information will no longer be used therefore the information will be kept for an indefinite length of time.

ADDITIONAL OPTIONAL TUMOR BIOLOGY CONSENT

This part of the study is optional. You can still be in the Nifurtimox study if you decide you don't want to be in this part of the study. If you agree to allow your samples to be stored for future research, your blood, bone marrow and tumor samples will be stored in a safe and confidential area for up to 20 years. You have the option to remove your samples from the laboratory at any time. If in future, if you ask that your stored samples be destroyed, it is important to know that any research that has already been done on the samples cannot be changed. No matter what you decide to do, it will not affect the care that you will get.

Because these tests are for research only, usually your study doctor or you will not know the results. It is very unlikely that the research testing might find important information about your current or future health. If this unlikely event happens, the researchers may contact your doctor about what the research test results might mean. Only your doctor will be notified and the information will not become part of your medical record. Your doctor may discuss this unexpected finding with you, and may recommend that you see a genetic counselor and/or repeat testing in a clinical (not research) laboratory if needed. It is possible that your doctor may decide that no action is needed.

I agree to have my blood, bone marrow and tumor samples, obtained as part of my regular care, sent to a special neuroblastoma/medulloblastoma laboratory for research studies that will not directly impact my treatment, but the results of these research studies may benefit future children with neuroblastoma or medulloblastoma.

YES_____ NO_____ (initials) Date_____/_____/_____

I agree to have any leftover blood, bone marrow and tumor samples from the above optional biology studies saved in a neuroblastoma/medulloblastoma laboratory to be used for cancer and/or Nifurtimox research in the future.

YES_____ NO_____ (initials) Date_____/_____/_____

Signature Block for *Minor* Participants:

Your signature below documents your permission for the child named below to take part in this research and to the use and disclosure of this child's protected health information. You will receive a signed copy of this complete form.

Printed name of child

Signature of parent or guardian

Date

Printed name of parent or guardian

❑ Parent
❑ Guardian (See note below)

Note on permission by guardians: An individual may provide permission for a child only if that individual can provide a written document indicating that he or she is legally authorized to consent to the child's general medical care. Attach the documentation to the signed document.

Signature of person obtaining consent

Date

Printed name of person obtaining consent

Signature Block for *Capable Adult* Participant:

Your signature below documents your permission to take part in this research and to the use and disclosure of your protected health information. You will receive a signed copy of this complete form.

Signature of participant

Date

Printed name of participant

Signature of person obtaining consent

Date

Printed name of person obtaining consent

Signature Block for Non-English Speaking: Short Form

Your signature below documents your permission to take part in this research and to the use and disclosure of your protected health information. You will receive a signed copy of this complete form.

Signature of participant	Date
Printed name of participant	
Signature of person obtaining consent	Date
Printed name of person obtaining consent	

I certify that I have interpreted, to the best of my ability, in the participant's stated primary language, all oral presentations made by all of those present during the informed consent discussion.

Signature of Interpreter	Date
Printed name of Interpreter	