SAMPLE INFORMED CONSENT

NANT 2012-01 PHASE I STUDY OF DIFLUOROMETHYLORNITHINE (DFMO) AND CELECOXIB WITH CYCLOPHOSPHAMIDE/TOPOTECAN FOR PATIENTS WITH RELAPSED OR REFRACTORY NEUROBLASTOMA

A New Approaches to Neuroblastoma Therapy (NANT) treatment protocol.

The word "you" used throughout this document refers to you or your child.

WHAT IS THIS STUDY ABOUT?

This study is a clinical trial, a type of research study. Clinical trials include only patients who choose to take part. Please take your time to make your decision about participating. You may discuss your decision with your friends, family, and health care team. If you have any questions, you may ask your study doctor.

You are being asked to participate in this study because you have been diagnosed with neuroblastoma, a type of solid cancer that usually affects children. Your cancer has either grown back (relapsed) or has never gone away (persistent tumor) after standard treatment. Standard treatment may have included chemotherapy, surgery, radiation therapy and/or high-dose chemotherapy with a stem cell transplant.

WHY IS THIS STUDY BEING DONE?

The purposes of this study are:

To find the highest dose of DFMO that can be given with celecoxib, cyclophosphamide and topotecan without causing severe side effects.

To find out the side effects seen by giving DFMO at different dose levels with celecoxib, cyclophosphamide and topotecan.

To measure the levels of DFMO in the blood at different dose levels.

To determine if your tumor gets smaller after treatment with DFMO, celecoxib, cyclophosphamide and topotecan.

To determine if specific gene changes in you or your tumor makes you more prone to side effects or affects your tumor's response to the combination of DFMO, celecoxib, cyclophosphamide and topotecan.

To determine if the amount of normal chemicals in your body called polyamines go down in response to DFMO, celecoxib, cyclophosphamide and topotecan, and whether you are more likely to have a good response to the treatment if they do.

The research is being done because:

Currently there is no known effective treatment for your type of cancer.

This study will combine an oral drug called DFMO with celecoxib and two chemotherapy medicines called cyclophosphamide and topotecan.

DFMO is an investigational drug that is not approved by the FDA for use in cancer patients, although it has been approved by the FDA for use against an infection called trypanosomiasis that can affect the brain. DFMO blocks the production of chemicals called polyamines that are important in the growth of cancer cells. This drug has been tested as a single-agent in adults with cancer and has had limited activity. It has not been tested in combination with chemotherapy in patients with childhood tumors. It is believed that polyamines may play a more important role in childhood tumors, particularly those that depend on the abnormal activity of MYC genes. In the laboratory, DFMO and celecoxib are able to reduce the growth of neuroblastoma tumors using models of this cancer in mice. This effect is even greater when DFMO and celecoxib are combined with chemotherapy drugs, including cyclophosphamide and topotecan.

Celecoxib is a non-steroidal anti-inflammatory medication that is FDA approved for inflammation associated conditions but not for cancer. It is given at the same dose and schedule as it would be used for inflammation. It has been shown to cooperate with DFMO to affect polyamine levels in cells.

Cyclophosphamide and topotecan are both FDA-approved chemotherapy drugs. These drugs are approved for the treatment of certain adult cancers, but have also been used to treat children with cancer. These drugs have been used in combination in many people with neuroblastoma. In some patients with neuroblastoma, this combination has reduced the amount of neuroblastoma.

Giving DFMO and celecoxib together with cyclophosphamide and topotecan may increase the effectiveness of this combination. We first need to find out the highest dose of DFMO that can be given safely together with celecoxib, cyclophosphamide and topotecan. This study will be the first study to test giving DFMO together with these drugs. Once we have found out the highest dose of DFMO that can be given with celecoxib, cyclophosphamide and topotecan, we will treat more patients with this combination to determine how safe and effective it is.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Between 2 and 30 people will take part in this study.

WHAT WILL HAPPEN TO ME IF I TAKE PART IN THIS STUDY?

Medical Tests Before You Begin the Study

You will need to have the following exams, tests or procedures to find out if you can be in the main part of the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. These tests will also be done at various times throughout the study and at the end of the study. The purpose of these tests is to see how well the treatment works and to measure the status of your neuroblastoma. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

Physical exam	Bone marrow tests[#]
Blood tests	Various scans*
Pregnancy test	Hearing tests
Urine tests	

[#]Bone marrow tests are done by inserting a needle into the hip bone to remove the marrow which is inside the bone.

* Various scans that are done for diagnosis and checking the response of the tumor to treatment. These may include CT and /or MRI scans, Bone scans and MIBG or PET scans. We will recommend scans specific for your case and we will answer your questions about these scans.

During the Study

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures during the study. They are part of regular cancer care except that the hearing tests are scheduled to be more frequent since moderate hearing loss has been seen in some patients taking high doses of DFMO for long periods of time.

Physical exam	Bone marrow tests
Blood tests and scans	Various scans
Pregnancy test	Hearing tests
Urine tests	

Treatment Plan

The treatment will be given in cycles that each last 21 days, with the exception of cycle 1 that will be 28 days. A diagram of one cycle is shown in the following figure.

Cycle 1 Only

Day	1-7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22-28
Cyclophosphamide		X	X	X	X	X										
Topotecan		X	X	X	X	X										
DFMO	X	X	X	X	X	X	X	X								X
Celecoxib	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Cycles 2 through 17*

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Cyclophosphamide	X	X	X	X	X																
Topotecan	X	X	X	X	X																
DFMO	X	X	X	X	X	X	X								X	X	X	X	X	X	X
Celecoxib	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

You will receive both cyclophosphamide and topotecan into the bloodstream (either through your central line or through a small tube placed in a vein in your hand or arm) on days 8-12 during cycle 1 and on days 1 through 5 during cycles 2-17. You will receive each medicine over 30 minutes and the cyclophosphamide will be given first. This medicine is typically given in the clinic.

You will receive celecoxib by mouth twice a day every day of each cycle. The medicine is most commonly given as a capsule. If you have a hard time swallowing capsules, the medicine can also be taken out of the capsule and swallowed with applesauce or in a prepared liquid mixture.

You will receive DFMO by mouth three times a day for 14 days surrounding the IV cyclophosphamide and topotecan days (days 1-7 and 15-21). On course 1 only, you will also receive this medicine by mouth three times a day on days 1-14 and days 22-28. The medicine is provided as a powder that can be dissolved in certain liquids like lemonade to make it easier to take. You will be provided with a handout that will give you information on how to mix it.

When you join the study, you will be assigned a certain DFMO dose. This study will test up to 4 DFMO doses in groups of 3-6 patients. The starting DFMO dose for the first group of patients is about 33% lower than what was given to adult patients receiving DFMO and chemotherapy without bad side effects. If this is tolerated without serious side effects, then the DFMO dose will be increased ("dose escalation") in groups of 3-6 patients until either serious side effects are seen or until the 4th dose level is completed and found to be safe. At that point, investigators will have found the highest dose of DFMO that can be

given along with celecoxib, cyclophosphamide and topotecan without bad side effects. This goal is what makes this a Phase I study.

The doses of celecoxib, cyclophosphamide and topotecan are not increased during this study. The doses used are typical doses used to treat inflammation (celecoxib) and patients with neuroblastoma (cyclophosphamide and topotecan).

After the highest dose of DFMO that can be given with celecoxib, cyclophosphamide and topotecan has been found, another group of 12 patients may be treated with that highest dose.

In addition, you will be given a medicine to help boost your white blood cell count. White blood cells help fight infection and having low white blood cells can increase your risk of developing an infection. This type of medicine is called filgrastim or GCSF and is given once a day as a shot under the skin until the white blood cell count has increased to a safe level. This usually takes about 10 days for each cycle of chemotherapy. Your doctor may give you a related medicine called pegfilgrastim that requires just one shot under the skin for each cycle of chemotherapy.

Depending on the side affects you have and/or the side effects other patients have had on this study, you may need to take medicines that block stomach acid to prevent stomach irritation. Your study doctor will discuss whether this is necessary for you and provide information on how these medications are given.

You can receive up to 17 cycles of treatment (approximately 1 year) as long as you are not having bad side effects and as long as your tumor is not getting worse. Although other participating patients may receive a different dose of DFMO, your assigned dose of DFMO will not change during your participation in this study unless you develop certain side effects that necessitate lowering your dose of DFMO.

When you have finished treatment with DFMO, celecoxib, cyclophosphamide and topotecan

After you stop treatment with DFMO, celecoxib, cyclophosphamide and topotecan, you will continue to have tests and scans done (listed below) to measure how much tumor is left. If test results show you have abnormal organ functions, tests will be repeated monthly until test results are stable or normal. You doctor will tell you how often these tests and evaluations will be done.

Medical Tests after the Study:

Physical exam	Bone marrow tests
Blood tests	Various scans
Urine tests	Hearing tests

A table detailing the tests and procedures required before, during, and after the study has been attached to the end of this consent.

Determining blood levels of DFMO

One of the goals of this study is to find out the amount of DFMO in the blood during this treatment. Since this is one of the main goals of the study, subjects are required to submit extra blood samples in order to participate in the overall study.

On four separate occasions after starting DFMO treatment (day 8and 12 of cycle 1 and day 1 and 5 of cycle 2), a small amount of blood (3 mL, or slightly less than a teaspoon) will be drawn. If you have a central line (such as a port or a Broviac), this sample can be drawn through that line. Otherwise, you will need to have blood drawn through a vein.

This amount of blood is considered safe to donate over this amount of time. Samples will be sent to the Children's Hospital of Philadelphia in Philadelphia, PA and the levels of DFMO in the blood will be determined.

Other Research Tests in this Study

You will be asked if you want to participate in optional research tests. **This part of the study is voluntary.** The results of these tests would not be told to you or your doctor or become part of your medical record. These results would also not be used to make decisions about your care while enrolled on this study. You can decide not to let the doctors do these tests and still be able to be treated as part of this clinical study. There are checkboxes on the next to last page of this consent form to mark whether you are willing to participate in these voluntary studies.

Evaluating a gene called *ODC1* that is the target of DFMO treatment

One part of the research goal is to look for a genetic change in the *ODC1* gene in normal blood cells of patients to see if these are related to how DFMO treatment affects your tumor, or whether you will have worse side effects after taking these drugs. We may also look to see if other genetic changes impact how likely a person is to respond to this drug combination also. These tests are done on one sample of blood (less than one teaspoon, 3 mL) taken from your central line (or port). This amount of blood is considered safe to donate. The blood will be sent to The Children's Hospital of Philadelphia in Philadelphia, PA for testing.

Measuring the amount of polyamines and related chemicals in your body

DFMO and celecoxib work together to deprive the cancer of the ability to make polyamines, chemicals that may be important for the tumor's survival and growth. Another research goal is to look at the amount of polyamines in your body while receiving these treatments to see if the amount of polyamine reduction is related to the likelihood of your tumor getting smaller or of developing side effects. These tests are done on urine samples obtained at different times while on treatment. Samples will be collected 4 times in cycle 1 and 2 times in cycle 2, and then a sample is collected approximately every 6 weeks afterwards as long as you continue to receive DFMO therapy. The urine will be sent to The Children's Hospital of Philadelphia in Philadelphia, PA for testing.

Measuring the amount of polyamines in your tumor cells

If your doctors remove tumor cells from you during the course of providing optimal care, we will request that any left-over sample be submitted so that we can measure the level of polyamines in the tumor cells. This might include a biopsy of the tumor, or removal of bone marrow that contains tumor cells.

HOW LONG WILL I BE ON THIS STUDY?

You can receive up to 17 cycles of treatment (approximately 1 year) as long as you are not having bad side effects and as long as your tumor is not getting worse.

After you stop treatment, you will continue to have tests and scans done to measure how much tumor is left. Your doctor will tell you how often these tests will be done. Researchers will continue to collect information about you for a lifetime. Information will be collected about whether you are still alive; whether your tumor has grown back and at what sites in the body; whether you have developed any side effects from the treatment; or whether you have developed any additional cancer. Your oncologist or family doctor will give the researchers this information at regular intervals.

CAN I STOP BEING IN THE STUDY?

Yes. If you are thinking about stopping the study, you should talk to your doctor before making a final decision so he/she can tell you how to do this safely.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow study rules; or if the study is stopped.

WHAT ARE THE RISKS OF THE STUDY?

This is a Phase I study. A Phase I study looks at how common and serious side effects can be for each patient at a specific dose of a drug. In a Phase I study, some patients may have very serious side effects and could die as a result of these side effects. You may be one of those patients who have serious side effects as a result of participating in this study.

In this study, researchers will be looking at side effects seen in patients taking different doses of DFMO together with celecoxib, cyclophosphamide and topotecan. Since subjects will be assigned to different doses of DFMO, some subjects may receive doses that are too small to be effective while others may receive higher doses that may cause increased side effects.

Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Other drugs may be given to make side effects less serious and more comfortable (such as for nausea, headache or itching). Many side effects go away soon after you stop taking DFMO, celecoxib, cyclophosphamide and topotecan, but it is always possible that side effects can be serious, long lasting or may never go away. There is also a risk of death. Patients are watched carefully and treatment will be stopped if bad side effects develop. Because this combination has never been given to children before, there may be risks we do not know about. You should talk to your doctor about any side effects that you have while taking part in this study. While on the study, you are at risk for the side effects listed on the following pages.

Possible side effects of difluoromethylornithine (DFMO)

- hearing loss or ringing in the ears (tinnitus)
- loss of appetite
- nausea and/or vomiting
- diarrhea
- 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
- headache
- sores in the mouth (stomatitis)
- generalized weakness (asthenia)
- rash
- muscle aches (myalgia)
- increased protein in the urine (albuminuria)

Possible side effects of Celecoxib:

Likely	Less Likely	Rare but serious
• You may be unaware of an infection when the white count is low (neutropenia) because you may not develop a fever while taking celecoxib	• Stomach ache or acid stomach • Diarrhea • Sore throat, inflammation of the sinuses and/or runny nose • Elevation in the blood of certain enzymes found in the liver which may indicate liver irritation or damage	• Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure, rapid heart rate chills and fever. This is more likely to happen if you have an allergy to Sulfa drugs or aspirin or have had asthma, nasal polyps and hives. • Excessive gas in the GI tract • Nausea • Headache • Dizziness • Mild rash • A low red blood cell count which could make you feel tired and weak • Fluid retention and build-up in the tissues usually of the lower legs leading to an increase in weight • 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 due to irritation of the gastrointestinal tract and/or from a stomach ulcer • Inflammation or damage to the liver which can be severe and life-threatening and which may lead to an enlarged liver, a yellow appearing skin, and fluid collection in the abdomen which makes it look larger. • Severe damage to the kidney which may be irreversible and lead to kidney failure • Drugs of this type called COX-2 inhibitors have been associated with severe cardiovascular events such as heart attack, high blood pressure or stroke. This is more likely to occur in patients who are older, who have had coronary artery surgery or who have diseases that make them more susceptible to events of this type.

Possible side effects of 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
	• 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
		• Temporary blurred vision
		• Nasal stuffiness with fast IV infusions
		• Irregular heart rate with fast IV infusions
		• Skin rash
		• Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure, rapid heart rate chills and fever
		• Abnormal hormone function which may lower the level of salt in the blood
		•
		• Heart muscle damage which may occur with very high doses and which may be fatal
		• Darkening of areas of the skin and finger nails
		• Fingernail changes
		• Slow healing of wounds
		• Infections
		• Infertility which is the inability to have children
		• 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

Possible side effects of Topotecan:

Likely	Less Likely	Rare But Serious

• Diarrhea
• Nausea
• Vomiting
• Constipation
• Fewer white blood cells, red blood cells and platelets in the blood.
  o A low number of white blood cells can make it easier to get infections
  o A low number of red blood cells can make you feel tired and weak
  o 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
	• Headache
	• Lack of muscle strength or weakness
	• Rash, hives, itching or a red bumpy rash
	• A mild lowering of the blood pressure which usually does not require treatment
	• Shortness of breath
	• Inflammation and/or sores in the mouth, throat and/or esophagus
	• Elevation in the blood of certain enzymes found in the liver which may indicate liver irritation or damage
	• An infection in the blood which will require admission to the hospital and treatment with antibiotics
		• 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.
		• Chest pain
		• Shaking chills
		• Elevation in the blood of certain enzymes or bilirubin found in the liver which could indicate liver irritation or damage
		• Numbness and tingling in the fingers and toes
		• Muscle or joint aches and pains
		• Bleeding into the tumor which may cause damage depending on the location of the tumor
		• Small amount of blood and/or protein in the urine or an elevation in blood creatinine which may indicate mild kidney damage

Possible side effects of Growth Factors (such as Neupogen, Filgrastim Or Neulasta, Pegfilgrastim)

Growth Factors are not anti-cancer medicines. It helps the growth of white blood cells that fight infection.

Neupogen (Filgrastim) Toxicity:

Likely (happens to 21-100 children out every 100 children)	**Less Likely (happens to 5-20 children out every 100 children)**	**Rare (happens to < 5 children out every 100 children)**
• Aching or pain in bones.	• Local irritation/pain at the site of the injection. • Higher than normal levels in the blood of uric acid and of liver enzymes which may indicate liver irritation or damage. • Fever • A low number of platelets in the blood which may cause you to bruise and bleed more easily.	• Allergic reactions which can be life threatening with shortness of breath , low blood pressure, rapid heart rate, hives, facial swelling. This reaction is very rare and has been associated mainly with intravenous administration. • If you are known to have sickle cell disease , this drug may cause sickle cell crises • Severe damage to the spleen (an organ in the abdomen which stores blood cells) which could lead to pain and loss of blood into the abdomen. Or rupture of the spleen. • Difficulty breathing and lung damage that may be due to the white blood cells, stimulated by Pegfilgrastim , travelling to the lungs when they are inflamed or infected (Adult Respiratory Distress Syndrome Bone marrow dysfunction (MDS) or secondary leukemia in patients with very bad ongoing low white cell counts that require prolonged administration of this drug. • Worsening of skin rashes • Low Fever • Inflammation of blood vessels leading to a raised purple rash and bruising • Higher than normal white blood count. • Low blood pressure and/or increased heart rate • Wheezing or shortness of breath • Skin rash, hives or facial swelling

Neulasta (Pegfilgrastim) Toxicity:

Likely (happens to 21-100 children out every 100 children)	**Less Likely** (happens to 5-20 children out every 100 children)	**Rare** (happens to < 5 children out every 100 children)
• Aching or pain in bones.	• Local irritation at the site of the injection. • Headache • Higher than normal levels in the blood of uric acid and of liver enzymes which may indicate liver irritation or damage. • A low number of platelets in the blood which may cause you to bruise and bleed more easily.	• Low grade fever • Allergic reactions which can be life threatening with shortness of breath, low blood pressure, rapid heart rate, hives, facial swelling. This reaction is very rare and has been associated mainly with intravenous administration. • Redness and flushing of the face and body. • Enlarged spleen • Severe damage to the spleen (an organ in the abdomen which stores blood cells) which could lead to pain and loss of blood into the abdomen. • If you are known to have sickle cell disease , this drug may cause sickle cell crises • Markedly higher than normal white blood cell count which may be associated with fever and red, often painful patches on the skin (Sweet's syndrome). • Difficulty breathing and lung damage that may be due to the white blood cells, stimulated by Pegfilgrastim, travelling to the lungs when they are inflamed or infected (Adult Respiratory Distress Syndrome)

Unknown frequency and timing: It is unknown whether filgrastim or pegfilgrastim produce birth defects or other serious abnormalities in the unborn child in humans as there is conflicting data from animal studies. It is also unknown whether these drugs are excreted in breast milk.

Possible risks to unborn child and nursing child

Patients who agree to participate in this study should not become pregnant or breast feed while on this study. This study and the medicines used in this study may be hazardous to an unborn child. Patients and their sexual partners should use abstinence and /or an effective method of contraception that is medically appropriate based on your personal doctor's recommendation at that time. If you or your partner becomes pregnant while you are participating in this study, please notify your study doctor immediately. For more information about risks and side effects, ask your study doctor.

Possible long term side effects of this treatment

- Recurrence of tumor
- Infection
- Sterility and/or delayed onset of sexual maturity
- Increased risk of a second cancer (such as leukemia) different from the kind of cancer you have now.

Possible risks from having blood drawn
The risks from having your blood taken are minimal, but can include an infection or a blood clot. Experienced doctors or nurses will perform these blood draws to minimize this risk. These have risks that will be discussed with you. You will be asked to sign a separate consent for any procedure that needs sedation.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

There may or may not be direct medical benefit to you. The information learned from this study may or may not benefit other children or young people with solid cancers in the future.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THIS STUDY?

Yes there are other options for treatment. Instead of being in this study, you have these options:

Treatment with chemotherapy medicines
Treatment with other experimental agents that may be available.
No therapy at this time, with care to help you feel more comfortable.

Please talk about these options with your doctor.

WILL MY MEDICAL INFORMATION BE KEPT PRIVATE?
We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance and data analysis include:
- New Approaches to Neuroblastoma Therapy (NANT) Consortium at Children's Hospital Los Angeles in Los Angeles, CA. The NANT Consortium identifies you by a number.
- Independent auditor evaluating quality assurance for the NANT Consortium.
- The National Cancer Institute (NCI) and other governmental agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people.
- Cancer Prevention Pharmaceuticals (drug patent holder of DFMO)

NANT has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. Information about the certificate is included at the end of this consent

WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?
Taking part in this study may lead to added costs to your insurance company. Your health insurance company will be billed for many expenses associated with the costs of this study. These expenses include medications, treatments, hospital/clinic charges, and doctors' fees related to your participation in this study.

Celecoxib, cyclophosphamide and topotecan are commercially available agents. You will pay for the amount of drugs needed to complete this study. This cost is normally covered by your insurance company.

Cancer Prevention Pharmaceuticals, holds the drug patent for DFMO. The drug will be manufactured and distributed by Sanofi-Aventis at no cost to you. A continuing supply of the drug cannot be guaranteed. If there is a problem getting DFMO, your study doctor will talk with you about possible options. If, during the study, DFMO becomes approved for use in your cancer, you and/or your health plan may have to pay for drug needed to complete this study.

The pharmacokinetic studies measuring DFMO levels, and the other optional tests looking at specific genes in you and/or your tumor, and at polyamine levels, will be done at no cost to you if you agree to participate in this voluntary study. However, you or your health plan may need to pay for the costs of the supplies and personnel who withdraw the blood from you for these tests.

You may have to pay for other things during this study, such as but not limited to, your time, the cost of food you buy while you are being treated at the hospital/clinic, car fare, travel to and from the hospital/clinic, parking, and baby sitter fees.

Taking part in this study may lead to added costs that may be covered by your insurance company. Please ask about any expected added costs or insurance problems.

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

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage . You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?

It is important that you tell your study doctor, _____ *[investigator's name(s)];* if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number].*

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

WHAT ARE MY RIGHTS AS A STUDY PARTICIPANT?

Taking part in this study is your choice. You may choose not to take part or not take part in the study. If you decide to take part in this study, you may remove yourself from the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. If you remove yourself from the study, we will still take care of you. We will explain what stopping the treatment may do and we will offer other treatments if they are available.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In case of injury resulting from this study, you do not lose any of you legal rights to seek payment by signing this form.

A Data Safety and Monitoring Board, an independent group of experts, will be reviewing data from this research throughout the study. We will tell you about new information from this Board or other studies that may affect your health or willingness to stay in the study.

WHO CAN ANSWER MY QUESTIONS ABOUT THE STUDY?
You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number].*

For questions about your rights while taking part in this study, call the _____ *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ *(telephone number).*

WHERE CAN I GET MORE INFORMATION?

You may call the NCI's **Cancer Information Service** at

1–800–4–CANCER (1–800–422–6237) or **TTY: 1–800–332–8615**

You may visit the NCI Web sites at http://cancer.gov/
For NCI's clinical trials information, go to **http://cancer.gov/clinicaltrials/**
For NCI's general information about cancer, go to **http://cancer.gov/cancerinfo/**

You will get a copy of this consent form. If you want more information about this study, ask your study doctor.

A description of this clinical trial will be available on http://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 website at any time.

CONSENTS FOR EXTRA STUDIES FOR RESEARCH

The following tests are optional for all patients in the study. You may still participate in the study even if you do not agree to these tests.

Evaluating a gene called *ODC1* that is the target of DFMO treatment

Initial next to YES, if you agree to let researchers take blood to study *ODC1*gene changes that may affect how well the DFMO works against your tumor or how likely side effects may be. This is one extra blood sample and it can be taken from a central line (such as port or Broviac). The results of these tests will be confidential and not made available to you or your treating physician.

Initial next to NO, if you do not want researchers to take an extra blood sample to study the *ODC1* gene.

_____ YES _____ NO

Measuring the amount of polyamines and related chemicals in your body

Initial next to YES, if you agree to let researchers take urine samples to measure the amount of polyamines and related chemicals in your body. This is to compare the amount of polyamine reduction in your body with the response of your tumor and whether you have side effects from treatment. The results of these tests will be confidential and not made available to you or your treating physician.

Initial next to NO, if you do not want researchers to take urine samples to measure the amount of polyamines and related chemicals in your body during DFMO treatment.

_____YES _____ NO

Measuring the amount of polyamines in your tumor cells

Initial next to YES, if you agree to let researchers send tumor or tumor-containing bone marrow from you to test (only if this is done in the course of providing optimal care for you). This is measure the amount of polyamines in your tumor cells while on treatment. The results of these tests will be confidential and not made available to you or your treating physician.

Initial next to NO, if you do not want researchers to take urine samples to measure the amount of polyamines and related chemicals in your body during DFMO treatment.

_____YES _____ NO

STATEMENT OF CONSENT

I have already read the information in this informed consent document. I have read all the attachments that were included with this informed consent document. I have asked all of my questions and I have gotten answers. I agree to enroll myself (my child) in this study.

_____
Patient Name

_____ _____/_____/_____
Signature of Parent or Guardian Date

_____ _____/_____/_____
Signature of Parent or Guardian Date

_____ _____/_____/_____
Signature of Patient (If > 7 years old) Date

_____ _____/_____/_____
Signature of Physician or Responsible Investigator Date

_____ ____/_____/_____
Signature of Witness Date

_____ ____/_____/_____
Signature of Translator (If applicable) Date

Consent Addendum #1: Tests that will be done on this study.

Observation	Before Entry	Cycle 1	Cycles 2-17	End of Therapy
Physical Examination	X	Weekly	Start of each cycle	X
Blood tests	X	Twice weekly	Weekly	X
Bone marrow tests*	X		Perform after cycle 2, 4, and 8 and after every 4 cycles thereafter	X
Hearing Tests			Perform after cycle 1, 2, 4, and 8 and after every 4 cycles thereafter	
Tumor scans (CT scan, MRI scan, Bone scans and/or MIBG scan)	X		Perform after cycle 2, 4, and 8 and after every 4 cycles thereafter	X
Blood for drug level tests (required)		Three times	One time in cycle 2	
Urine to measure polyamines (optional)		Four times	One time in cycle 2 and one time every other cycle	Urine to measure polyamines
Blood to check for ODC1 gene change involved in polyamine metabolism and DFMO effect (optional)		X		
Optional Tissue Sampling		One time during the study		

*Additional testing may be done on bone marrow collected if the bone marrow has enough tumor and you have consented to do this. This part of the study is optional.

Consent Addendum #2

Certificate of Confidentiality Information

NANT has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. The Certificate protects against the involuntary release of information about subjects collected during the course of our covered studies. The researchers involved in the studies cannot be forced to disclose the identity or any information collected in the study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, the subject or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if the subject or his/her guardian requests the release of information in writing, the Certificate does not protect against that voluntary disclosure. Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act. The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

SAMPLE ASSENT FORM

PHASE I STUDY OF DIFLUOROMETHYLORNITHINE (DFMO) AND CELECOXIB WITH CYCLOPHOSPHAMIDE/TOPOTECAN FOR PATIENTS WITH RELAPSED OR REFRACTORY NEUROBLASTOMA

A New Approaches to Neuroblastoma Therapy (NANT) treatment protocol

INVESTIGATOR [Insert Name of Investigator]
[Insert Name of Institution]

[Insert Address (include City, State and Zip Code)]
[Insert Telephone/Fax Numbers]
[Insert Email]

1. My name is _____.

2. You have a kind of cancer called **Neuroblastoma.** We are asking you to take part in a research study because doctors want to learn more about treating neuroblastoma using four medicines called **DFMO, celecoxib, cyclophosphamide and topotecan** to see what effects (both good and bad) these medicines have on patients and their cancer. DFMO and celecoxib are medicines that are given by mouth as a pill (tablet) or in a liquid mix. Cyclophosphamide and topotecan are medicines given into the bloodstream (either through your central line or through a small tube placed in a vein in your hand or arm). The doctors think that giving these four drugs together may kill neuroblastoma cancer cells.

3. If you agree to be in this study this is what will happen:

   The medicines will be given in cycles that each last 21 days, in addition to the first cycle which is 28 days. You will continue to receive up to 17 cycles (approximately 1 year or a little longer) of this treatment unless you have bad side effects or your tumor gets worse.

   DFMO:
   You will take DFMO by mouth three times a day for 14 days of every 21 day cycle (28 days in cycle 1).
   Celecoxib:
   You will take celecoxib by mouth twice a day each day of every 21 day cycle (28 days in cycle 1).
   .
   Cyclophosphamide and Topotecan:
   You will take cyclophosphamide and topotecan by vein once a day for 5 days every 21 day cycle (28 days in cycle 1).

   Other medicines (not chemotherapy):
   You will need to take Neupogen (given once daily under your skin) or Neulasta (give one time under your skin) to help your normal blood cells get better after chemotherapy.
   You may need to take other medicines to help you with side effects of the medicines above.

   Coming to See the Doctors:
   During and after you have finished the treatment, you will have appointments with the doctors who are taking care of you. This is called "**Follow-Up**". This is to see how well the treatment has worked so far. The doctors will want to do some special tests to find this information out. They will include;
   - Blood tests (we will do this twice each week to start with, and then less often)
   - MRI, CT, Bone and MIBG Scans (special pictures of your tumor)
   - Bone marrow test (to look for tumor in your bone marrow)
   - Feel your belly, look into your eyes and ears, and listen to your heart and lungs.

- Ask you and your parents a lot of questions about how you are feeling, how you are doing in school, and any problems you might be having.
- You may have to come to the clinic to have blood and platelet transfusions when the blood counts are low or stay in the hospital if you have a fever with low blood counts.

You will come to visit your doctor every week or so to start with, then less often if everything is going well.

4. Sometimes things happen to kids in research studies that may make them feel bad. These are called "risks'. Some of the risks of this study are:
   - You may feel sick to your stomach and you may throw up.
   - You may feel tired.
   - You may have a bad appetite.
   - You might have a fever and maybe an infection where you will need to be in the hospital to get medicines to treat the infection. You may feel tired and weak and need a blood transfusion or you may get bruises or have bleeding (most often a nosebleed) and need a platelet transfusion.
   - You may get sores in your mouth that makes it difficult to eat and drink. If this happens, you may need some pain medicines and you may need to stay in the hospital.
   - You may get diarrhea.
   - The treatments may not work, and your tumor may grow, or it might come back again after the treatment has finished. If this happens we will try other ways to stop the tumor from growing.
   - You could get a different kind of cancer, this doesn't happen often, but can happen years later.
   - You could have problems with your hearing that might be temporary or permanent.
   - It is possible that you could die from the treatment or cancer.

Not all of these things may happen to you. Or things may happen that the doctors don't know about yet.

5. People also have good things that happen to them when they are in research studies. These are called "benefits". The benefits to you of being in this research study are that this treatment might make your neuroblastoma tumor stay the same size or get smaller for some time. We hope to learn more about this new treatment which could help other children with neuroblastoma.

6. Please talk this over with your parents before you decide whether or not to be in this study. We will also ask your parents to give their permission for you to take part in this study. But even if your parents say "yes" you can still decide not to do this.

7. Being in this study is up to you. You do not have to be in this study if you don't want to. You may stop being in this study at any time.

8. You can ask any questions that you have about the study. If you have a question later that you didn't think of now, you can call me or ask me next time. Study doctor's phone number: _____.

9. Special study tests :

You will need to have some special blood tests done to measure the amount of medicine in your blood. You may need to have a needle poke or a small plastic tube placed in a vein of your hand or arm for these samples. If you have a central line, your doctor will be able to tell you if that can be used to draw these bloods.

You will also have the option of giving extra blood and urine samples. There are one blood and numerous urine samples which you don't need to agree to provide to be on this study. If you do not have a central line, then you would need to have a needle poke or a small plastic tube placed in a vein of your hand or arm for the blood sample.

- _____Yes, it is okay to take an extra blood samples even if a needle poke is required
- _____ Yes, it is okay to take an extra blood sample, but only if they can be taken from my central line
- _____ No, it is not okay to take a blood sample
- _____Yes, it is okay to take urine samples
- _____No, it is not okay to take urine samples

10. Signing your name at the bottom means that you agree to be in this study. You and your parents will be given a copy of this form after you have signed it.

Name of Subject: _____

_____ _____
Signature of Subject: **Date**

_____ _____
Signature of Investigator **Date**

_____ _____
Signature of Person Conducting Discussion **Date**