NMTRC 010B

RESEARCH SUBJECT INFORMATION AND CONSENT FORM	
TITLE:	A Phase I/II Trial of DFMO in Combination with Bortezomib in Patients with Relapsed or Refractory Neuroblastoma

This consent form contains important information to help you decide whether to participate in a research study.

In this consent form, "you" always refers to the subject. If you are a parent or guardian, please remember that "you" refers to the study subject.

The study staff will explain this study to you. Ask questions about anything that is not clear at any time. You may take home an unsigned copy of this consent form to think about and discuss with family or friends.

- **Being in a study is voluntary – <u>your choice</u>.**
- **If you join this study, you can still <u>stop at any time</u>.**
- **<u>No</u> one can <u>promise</u> that a study will help you.**
- **Do not join this study unless all of your <u>questions</u> are <u>answered</u>.**

After reading and discussing the information in this consent form you should know:

- Why this research study is being done;
- What will happen during the study;
- Any possible benefits to you;
- The possible risks to you;
- Other options you could choose instead of being in this study;
- How your personal health information will be treated during the study and after the study is over;
- Whether being in this study could involve any cost to you; and
- What to do if you have problems or questions about this study.

<u>Please read this consent form carefully.</u>

INFORMED CONSENT / PARENTAL PERMISSION FOR PARTICIPATION IN RESEARCH

TITLE: A Phase I/II Trial of DFMO in Combination with Bortezomib in Patients with Relapsed or Refractory Neuroblastoma

PROTOCOL NO.: NMTRC 010B
WIRB® Protocol #20140498

SPONSOR: Giselle Sholler, M.D.

INVESTIGATOR: Name
Address
City, State Zip
Country

SITE(S): Name
Address
City, State Zip
Country

STUDY-RELATED PHONE NUMBER(S): Name(s)
PhoneNumber(s) (24 hour phone number required)

In this consent form "you" means the child. Some children may also be asked to assent to take part in the study.

You are being invited to participate in a research study conducted by the Neuroblastoma and Medulloblastoma Translational Research Consortium (NMTRC). The NMTRC is a collaboration of academic medical centers and other organizations around the country. Helen DeVos Children's Hospital, a member of Spectrum Health Hospitals, serves as the lead organization of the NMTRC.

You are being invited to take part in this research study because you have a cancer called neuroblastoma that has come back after upfront treatment or did not respond to upfront treatment (called relapsed or refractory neuroblastoma).

In order to decide whether or not you should agree to be part of this research study, you should know enough about its risks and benefits in order to make a sound judgment. This process is known as informed consent. This consent form gives you detailed information about the research study. Once you understand the study, its risks, and its benefits, you will be asked to sign the form if you wish to take part. You will be given a copy to keep.

We encourage you to ask questions and take the opportunity to discuss the study with anybody you think can help you make this decision.

Why is This Research Study Being Conducted?

The purpose of this research study is to evaluate an investigational drug (DFMO) in combination with bortezomib, for relapsed and refractory neuroblastoma. DFMO is an investigational drug because it has not been approved by the U.S. Food and Drug Administration (FDA). Bortezomib, although a drug approved by the FDA for other cancers, is investigational for treatment of neuroblastoma in this study. This study will look at the safety and tolerability of DFMO in combination with bortezomib as well as the tumors response to this study drug.

DFMO was shown to be effective in inhibiting tumor growth in adult colon cancers. DFMO has been tested in multiple adult clinical trials and one pediatric trial. Laboratory testing in neuroblastoma suggests that this drug may be effective in treating this disease.

Subjects signing this consent form will be given a new formulation of DFMO that has not previously been used in children. This new formulation contains the same active ingredient as the previous formulation; however it is made by a different manufacturer and so it is possible that the DFMO may be absorbed differently by the body.

The first portion of this study is a Phase I trial. A phase I trial is a trial that is in the first stage of testing in human subjects. The purpose of a Phase I study is to test for safety and to find the highest dose of the drug that subjects can tolerate (optimal dosing). Optimal dosing of DFMO in combination with bortezomib in pediatric patients is not known at this time. This is the first time DFMO has been given with bortezomib to children. Read the sections on risks and benefits carefully and be sure you understand them.

This study will be using increasing doses that will continue until unacceptable toxicities are identified. If there are toxicities in one group of subjects, that dose may be repeated. There will be a hold in enrollment after each 3 subjects (each cohort) are enrolled in order to monitor that dose for safety and toxicities.

All children will receive the same dose of bortezomib.

Because of the way subjects are enrolled, there is a possibility that even if you qualify for this study, there may not be a space available for you to start on study.

You may receive a different dose of DFMO than other subjects depending on when you start on study. We cannot guarantee the dose that you will be given until you start on the study. Both you and the study doctor will know what dose you receive. The dose you receive may be so low that it has no effect or so high that you have side effects you cannot tolerate.

How Many People Will Take Part In The Study?

In this study, approximately 38 to 62 subjects will participate from about 15 medical centers across the United States. Approximately 5 of these subjects will be at the [INSERT INSTITUTION NAME HERE].

What Is Involved In The Study?

Screening:

You will undergo a number of standard tests and research-related procedures before being able to enroll in this study. You will need to have the following exams, tests and procedures to find out if you can be in the study. The results of these studies may show that you are not eligible to take part in this study. Most of these exams, tests and procedures are part of regular neuroblastoma care and may be done even if you do not join the study. Some procedures are being done only for research purposes as part of this study. Those tests are also listed below. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

Tests to be performed within 5 days of starting study:

- Medical history
- Physical exam
- Vital signs (blood pressure, pulse, temperature)
- Blood tests
- Urine tests (including a pregnancy test for girls who can become pregnant {age 13 or greater, or has started menstruation})

Tests to be performed within 21 days of starting study:

- MRI or CT scan of the tumor(s)
- Any other imaging studies or tests deemed necessary for assessing your tumor by your treating physician
- MIBG or PET scan. An MIBG scan involves injecting a radioisotope into the blood on the first day, and then scanning the whole body on the second day to see where the isotope was absorbed.
- Bone marrow aspirations and examination (this involves using a needle to extract a small amount of your bone marrow from both of your hips usually under anesthesia; at the time of your procedure you will be asked to sign a consent form for the anesthesia). We will ask you if we can collect a small amount of additional bone marrow that will be used for special research testing of neuroblastoma cells if they are present. (There is a separate consent for this at the end of this form.)

Tests to be performed for research related purposes only include:

- Audiogram; a hearing test that can detect hearing loss that is not noticed in daily conversation
- Urine samples (additional samples are voluntary)
- Additional samples of your Bone marrow aspirations as noted above (additional samples are voluntary)
- Additional samples of your blood (additional samples are voluntary)

As part of this study you will have an audiogram (hearing test) performed before you start taking the study drug and again at the end of cycles 2, 6, and then yearly. An

audiogram may also be requested by the study doctor at any time to check for changes in your hearing.

Study Treatment:

If the exams, tests and procedures show that you can be in the study, and you choose to take part, DFMO and bortezomib will be started in clinic on Day 1. You will take DFMO orally, by mouth, twice a day. DFMO will be provided to you as a tablet. If you are unable to swallow tablets you will need to crush them and mix with water or other liquid to then drink. Bortezomib will be given to you intravenously (IV).

You will be in clinic on this first day for approximately 3 to 5 hours. After this, you will be given the DFMO to take home and you will take it each day as prescribed for as long as you are in this study, unless you have side effects from the medicine or your tumor worsens. You will return to clinic on days 4 and 8 to receive bortezomib again, and will also return to clinic on day 15 for a physical exam during every cycle while in this study. These visits will last about 2 hours.

DFMO and bortezomib will be given to you in six individual cycles (courses) of therapy. Each course of therapy lasts 21 days; this is what we call a “cycle”. Each cycle will occur immediately after the last. This means that since each cycle is 21 days long, on day 22 you will be starting the next cycle.

At the beginning of each new cycle you will have some of these tests repeated including:

- Medical history
- Physical exam
- Vital signs (blood pressure, pulse, temperature)
- Blood tests
- Urine tests (including a pregnancy test for girls who can become pregnant)
- Any other imaging studies or tests deemed necessary for assessing your tumor by your study doctor

Additionally at the end of every two cycles you will also have the following procedures repeated:

- MRI or CT scan of the tumor(s)
- MIBG or PET scan.
- Bone marrow aspirations and examination (We will ask you if we can collect a small amount of additional bone marrow that will be used for special research testing of neuroblastoma cells if they are present. There is a separate consent for this at the end of this form.)

If your cancer is responding and if you are not experiencing unacceptable side effects from treatment, it will be up to your study doctor’s discretion to continue treatment on protocol beyond the six 21-day cycles of treatment described above (you may continue this until you have progression, you no longer wish to continue, or your study doctor decides it is not in your best interest). If you continue on drug past the six 21 day cycles, you will still be considered part of the study and you will still need to have

procedures done with every cycle as explained above. These follow ups include the same tests and procedures as the preceding cycles did. We will also continue to collect information from these tests and procedures and on your treatment and outcomes.

As a part of your treatment you may have a surgical operation to remove as much of the tumor as possible. You will be asked by the pediatric surgeon to sign a separate surgical consent form, which will review the risks of that surgical procedure. If the tumor is obtained by surgery for routine (non-study) care, you will be asked if some of the tumor can be saved for special research testing of cancer cells if they are present. There is a separate consent for this at the end of this form.

After you are finished taking DFMO, the study doctor will ask you to visit the office for a follow-up visit about 30 days after your last dose of DFMO. During this follow up visit you will have a physical exam, blood tests, urine tests, bone marrow test, and radiologic evaluations (MIBG scan {if done at screening}, CT scans and/or MRI) to assess the response of the tumor. You will then be followed to see how you are doing every 3 months for one year, then yearly until 5 years after stopping the study drug. We will do this follow up either by phone or e-mail.

All required radiology scans (MIBG's, PET's and MRI/CT's), must be done at the study institution, [INSERT INSTITUTION NAME] unless otherwise approved by the sponsor. If [INSERT INSTITUTION NAME] is not your home institution, all other care (excluding the previously mentioned) can be done at your home institution at the discretion of your study doctor.

Methods for Providing/Administering Study Drug

DFMO will be taken orally (by mouth) twice a day, once in the morning and once in the evening every day that you are on the study. DFMO is a tablet that will be supplied to you. If you cannot swallow tablets you will be given instructions on how to crush and take the study drug. DFMO may not be mixed with orange or grapefruit juice. You will be given a handout that will have the directions written out as well as a list of recommended juices and foods to use when mixing the DFMO. This handout will also include instructions for storing DFMO.

Bortezomib will be given intravenously (by IV) once a day on days 1, 4, and 8 of each 21 day cycle.

You will be asked to keep a daily diary of the study drug and dose you are taking; this diary will be provided to you by the study doctor, and will need to be returned to the study doctor at the end of each cycle.

Throughout the study, you will be asked to report any difficulties or side effects that you experience, regardless of whether or not you feel they are related to, or caused by, the study medication. It is very important for you to discuss any difficulties or side effects with your study doctor.

If you have any significant side effects or problems, you should promptly contact your home treating oncologist. Your home treating oncologist will then decide if you should come in to the hospital. In addition you will need to contact your study doctor. Your study doctor will determine what you should do about your study drug doses. Doses may be reduced, delayed or omitted if you have toxicities or side effects. If your condition worsens during the study, your study doctor may remove you from the study.

While you are on this study, there are certain medications and treatments that you will not be allowed to take. Those include any other cancer killing agents or chemotherapy, any other investigational (study) drugs, immunotherapy, hormonal therapy, and targeted therapies. Please discuss all medications that you are currently taking or wish to take with your study doctor.

PROCEDURES AND ASSESSMENTS FOR THIS STUDY

	Pre	Cycles 1				Cycles 2-6					Subsequent Cycles	Follow Up
		Day 1	Day 4	Day 8	Day 15	Day 1	Day 4	Day 8	Day 15	End of Cycle		
Informed consent	X											
Prior therapy review	X	X										
Physical examination and history		X	X	X	X	X		X	X		X	X
Lansky Score	X					X					X	X
Vital signs		X	X	X	X	X	X	X	X		X	X
Blood tests	X	X[a]		X	X	X		X	X		X	X
Pregnancy test if indicated	X	X[a]				X					X	
CT or MRI Scan	X									X[b]	X[b]	X[b]
MIBG or PET	X									X[b]	X[b]	X[b]
Review of Current Medications	X	X	X	X	X	X	X	X	X		X	X
Administration of DFMO[c]		X	→	→	→	→	→	→	→	→	→	
Administration of Bortezomib[d]		X	X	X		X	X	X			X[d]	
Dispense (and collect) drug dosing diary		X				X						X[e]
Adverse Event monitoring		X	X	X	X	X	X	X	X		X	X
Progression free Survival												X

Urine Tests	**X**				**X**	**X**					**X**	**X**
Audiogram (hearing test)	**X**									**X[f]**	**X[f]**	**X[f]**
Bone Marrow^	**X**									**X[b]**	**X[b]**	**X[b]**
Optional Blood Samples^		**X**			**X**	**X**						
Optional Urine Samples^		**X**			**X**	**X**						

[a] ***If not already done in the 5 days prior to first dose of drug***
[b] ***At end of cycles 2, 4, and 6, then every 2 cycles and as clinically indicated***
[c] ***DFMO given twice daily every day on study unless a hold is indicated***
[d] ***Bortezomib given on Days 1, 4, and 8 of each cycle unless a hold is indicated***
[e] ***If early withdrawal or not previously collected***
[f] ***At the ends of cycles 2, 6 and then yearly or as indicated***
^Separate consent at end for additional samples

What Are The Risks and Discomforts Of The Study?

You may have side effects while on the study. Everyone taking part in the study will be carefully watched for any side effects. However, study doctors do not know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the study drug. In some cases, side effects can be serious, long lasting, may never go away, or may even cause death. You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks of DFMO:

The risks of DFMO are not completely known in the pediatric population. That is one reason that this study is being done.

From previous Pediatric studies in Neuroblastoma:

Likely Happens to 10 - 30 subjects out of every 100	**Less Likely** Happens to 3 - 10 subjects out of every 100	**Rare** Happens to fewer than 3 subjects out of every 100

• Elevation in the blood of certain enzymes or bilirubin which could indicate liver irritation or damage	• Fewer red and white blood cells
	  ○ a low number of red blood cells can make you feel tired and weak and may require transfusion.
	  ○ a low number of white blood cells can make it easier to get infections
		• Abdominal Pain
		• Hair Loss or Thinning
		• Loss of appetite
		• Cough
		• Runny or stuffy nose
		• Conjunctivitis (infection of the conjunctiva of the eye)
		• Constipation
		• Fever
		• Emotional ups and downs
		• Headache
		• Pain

	• Decrease in the number of platelets made in the bone marrow which may cause bruising or bleeding • Infections • Diarrhea • Hearing Loss	• Skin Rash • Difficulty sleeping • Vomiting • Urinary retention • Reflux

From the adult studies on DFMO, the risks that were seen:

Most Likely Happens to 10 - 30 subjects out of every 100	**Likely** Happens to 3 - 10 subjects out of every 100	**Less Likely** Happens to fewer than 3 subjects out of every 100

• Fewer red and white blood cells
  ○ a low number of red blood cells can make you feel tired and weak and may require transfusion.
  ○ a low number of white blood cells can make it easier to get infections
• Decrease in the number of platelets made in the bone marrow which may cause bruising or bleeding
	• Nausea
	• Hearing Loss
	• Ringing in ears
	• Diarrhea
	• Headache
	• Weakness
		• Loss of appetite
		• Abdominal Pain
		• Flatulence (gas)
		• Dizziness
		• Skin Rash
		• Seizures
		• Sores in the mouth
		• Runny nose
		• Difficulty sleeping
		• Infections
		• Dry mouth
		• Constipation
		• Dry skin
		• Menstrual disorders
		• Sore throat
		• Vomiting
		• Vasodilation (the relaxation of blood vessels possibly causing low blood pressure)
		• Emotional ups and downs
		• Itchiness
		• Body aches
		• Pain

Hearing loss has been a noted side effect of DFMO in adult studies. Although much of this hearing loss was reversible upon stopping the study drug, there is limited experience in subjects that have hearing loss prior to starting the study. The standard chemotherapy for neuroblastomas that you previously received may also have caused hearing loss. The effects of DFMO on prior hearing loss are unknown. There is also no experience in a pediatric population which may differ from adults. This potential hearing loss may be permanent and irreversible.

The chance of having side effects and the severity of side effects may increase with higher doses of DFMO. All subjects will be monitored closely and will be evaluated for any signs of early side effects.

Certain other drugs may interfere with DFMO. Please check with the study doctor before starting ANY new medication or treatment.

Risks and side effects related to <u>Bortezomib</u> include those which are:

Most Likely Happens to 10 - 30 subjects out of every 100	**Likely** Happens to 3 - 10 subjects out of every 100	**Less Likely** Happens to fewer than 3 subjects out of every 100

• A feeling of weakness and/or tiredness
• Nausea and/or vomiting
• Constipation or diarrhea
• Loss of appetite
• Fever
• Fewer red blood cells and platelets in the blood
  ○ 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
• Fluid retention and build-up in the arms and legs leading to swelling and an increase in weight
• Infection
• Nerve damage that may cause pain, burning, numbness, and
	• Low blood pressure
	• Dizziness
	• Fainting
	• Difficulty sleeping or falling asleep
	• Chills including shaking chills
	• Skin rash with the presence of macules (flat discolored area) and papules (raised bump)
	• Excessive loss of water from the body
	• Acid or upset stomach (heartburn)
	• Pain which may be in the abdomen (belly), back, bone, head, joints, arms and legs, muscles, and nerves
	• Headache or head pain
	• Cough and/or shortness of breath due to inflammation in the lungs. (interstitial pneumonitis)
	• Fewer white blood cells in the blood
	  ○ a low number of white blood cells can make it easier to get infections
	• Low numbers of white blood cells called lymphocytes that may last a long time and make it easier to get infections which may be life threatening
	• A stoppage (or blockage) of the intestine which may require treatment
	• Inflammation and/or sores in the mouth and/or throat that may make swallowing difficult and are painful (painful mouth sores)
	• Bleeding in the gut that may show in the stools
	• Nose bleed
		• A hole in the intestines which would cause leakage into the abdomen (belly) with pain and infection
		• Damage to the brain associated with high blood pressure which may lead to difficulty thinking, carrying out normal tasks, headache, seizures (convulsions), difficulty seeing, blindness, or other visual changes, which if caught early can be reversed
		• Severe damage to the brain tissue which could lead to difficulty carrying out normal daily tasks or could lead to coma
		• Severe kidney damage (which

tingling in the hands and feet and may affect the ability to perform tasks that require fine movements • Nerve damage that may cause muscle weakness or paralysis in the hands and feet and may affect the ability to perform tasks that require fine movements	• Fever with a low white blood cell count which could indicate infection and may require hospitalization and treatment with antibiotics • Infection caused by hard to treat bugs including bacteria, virus, and fungus • Muscle weakness of the whole body • Anxiety • Blurred vision • Fluid build-up in the lungs that can make you feel short of breath due to heart muscle injury.	may be permanent) • Possible liver injury

Green tea, ascorbic acid (vitamin C), and other antioxidants may decrease the activity of bortezomib. To avoid the interaction, you should stop taking the following products/foods from one day before the start of bortezomib until 3 days after the last dose of bortezomib:

1. Green tea and its components
2. Vitamin products containing vitamin C and antioxidants
3. Foods with high vitamin C content, such as fruits
4. Herbal products and any products containing flavonoids or other antioxidant compounds

Please talk to your study doctor before starting any new medications or herbal supplements and before making a significant change in your diet.

Drinking grapefruit juice or eating grapefruit may increase the concentration of bortezomib in the blood. Therefore, eating grapefruit or drinking its juice should be avoided for the duration of treatment with bortezomib.

<u>Risks of Blood Draws:</u>

Risks associated with drawing blood are slight, but some risks include: pain, excessive bleeding, fainting or feeling lightheaded, bruising, infection (a slight risk any time the skin is broken), and multiple punctures to locate veins.

Blood will be drawn from a central line whenever possible to minimize these risks.

<u>Risks of Bone Marrow Aspiration:</u>

During this study, a sample of bone marrow will be collected from your hip bone(s) for testing (occasionally another bone is selected); this is usually done under anesthesia. Once you are under the anesthesia, a special needle will be inserted into the bone to collect the marrow. Pressure may be felt as the needle is inserted into the bone. There is a sharp sucking sensation as the marrow is aspirated, which lasts for only a few

moments. There may be some bleeding at the puncture site. You may experience discomfort or pain. More serious risks, such as serious bleeding or infection, are very rare.

Reproductive Risks:

DFMO was damaging to developing embryos in animal studies. Because the effects of DFMO on an unborn child or nursing infant are not known you may not take part in this study if you are pregnant or breastfeeding. Girls who can become pregnant (age 13 or older or have started having menses) who enter the study must have a negative pregnancy test prior to entry and during the study. Additionally, the effects of DFMO on sperm are not known. If you are a girl who can become pregnant or a male able to father children, you must use an acceptable method of birth control during the study to prevent pregnancy.

Both men and women should 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. Talk to your study doctor to decide what type of birth control is acceptable.

A possible effect of this study is the possibility of sterility (inability to have children).

If you suspect that you have become pregnant during this study, you must notify the research team immediately. You will be withdrawn from the study if you become pregnant.

For more information about risks and side effects, ask your study doctor.

You will be informed as additional information is discovered about how the study drug may affect the risk and/or your willingness to continue to participate in this study. Your study doctor will inform you of all known risks; however, there may be physical, mental or genetic adverse risks that are not known at this time.

What Are The Benefits of Participating In The Study?

Taking part in this study may or may not make your health better. While benefit is possible, participation may not benefit you and your health could worsen during this study.

We do know that the information from this study will help doctors learn more about DFMO as a treatment for cancer. This information could help future cancer patients.

What Other Options Are There?

Your other choices may include:

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting no specific treatment
- You can receive bortezomib off-study without receiving DFMO

You should talk to your home treating oncologist about your choices before you decide if you will take part in this study.

Are There Any Costs?

Taking part in this study may lead to added costs to you or your insurance company. Your study doctor will discuss any expected added costs that may be billed to you or your insurance provider.

The study drug, DFMO, will be provided free of charge by the NMTRC, while you are participating in this study. However, even though it is unlikely, there is a possibility that the supply of study drug may run out. If this happens, your study doctor will talk with you. You may have to be taken off study. Or, if the drug becomes commercially available, you may be able to obtain additional drug from the manufacturer and you or your insurance may be asked to pay for it.

You or your insurance company will be charged for continuing standard medical care and/or hospitalization. You or your insurance company will be responsible for charges for other drugs (including the bortezomib), hospitalizations, clinic visits, x-rays lab tests, etc.

You might have unexpected expenses from being in this research study. These charges may be submitted to your health insurance. However, your health insurance may not pay these charges because you are in a research study. In addition, if you are injured as a direct result of being in this study your insurance company may not pay to treat these injuries. Ask the study doctor for more information about this. We also encourage you to determine your health insurer's policy about paying for treatment in a research study.

Participating in this study requires that you visit the study hospital [INSERT HOSPITAL NAME HERE] multiple times over the course of the full study for evaluations (physical exam, blood draw, urine analysis, etc.) and scans (MRI/CT, MIBG/PET).

Is There Any Compensation?

There is no payment for participating in this study.

Can You Withdraw or Be Withdrawn From This Study?

Participation in this study is voluntary. You are not obligated to participate in this research. You are free to withdraw your consent at any time. Your withdrawal, or refusal

to participate, will not affect your current or future medical care in any way. Your decision will not result in any penalty or loss of benefits to which you are entitled.

It is important to tell the study doctor if you are thinking about stopping so any risks from the study drug can be evaluated by your study doctor. Another reason to tell your study doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

You will be told of any significant new findings that develop during the study that may affect your willingness to participate in the study. You may be asked to sign a new consent form to continue in the study.

Your study doctor or the sponsor may decide to take you out of the study at any time without your consent if any of the following occur or for other reasons:

- You do not meet the criteria to take part in the study.
- The side effects of the study drug are too harmful for you.
- You need a treatment that is not allowed on this study.
- Your tumor worsens.
- You become pregnant.
- The study doctor believes it is in your best interest.
- New information becomes available that would suggest that continuing in this study would not be in your best interest.
- You do not consent to continue in the study after being told of changes in the research that may affect you.
- The study is stopped.
- Or for any other reason.

The Neuroblastoma and Medulloblastoma Translational Research Consortium, Spectrum Health Hospitals, KC Pharma (the maker of DFMO), Western Institutional Review Board, or the FDA has the right to stop this study at any time. They may stop the study without your agreement based on medical information available to them.

<u>What About Confidentiality?</u>

We will do our best to make sure that your personal medical information 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.

Each subject in this trial will be identified by a unique identifier that will be used on all report forms and any other material submitted to the NMTRC. Report Forms for this study will be both paper and electronic. Electronic data will be stored in a secure data center. Your medical records are available to those caring for you at this hospital. Other people

or groups who may see or copy your medical record because you are participating in this study include:

- The Neuroblastoma and Medulloblastoma Translational Research Consortium (NMTRC), affiliates of the NMTRC, and the NMTRC010B study committee
- Spectrum Health Hospitals and its affiliates
- KC Pharma and their affiliates
- The U.S. Food and Drug Administration
- The Western Institutional Review Board® (WIRB®)
- The Spectrum Health Institutional Review Board
- Department of Health and Human Services (DHHS) agencies

Otherwise your name and other medical information that identifies you will not be released without your written permission, unless required by law. If results of this study are published, your identity will remain confidential.

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

Please refer to the separate authorization (HIPAA) form that explains more specifically how your personal health information will be used.

What Happens If You Are Injured?

Participating in research may result in an injury or illness. Medical treatment related to an injury or illness will be available at your treating institution, but such treatment may not be free of charge. No funding has been set aside to pay for the costs of treating an injury or illness that results from this study. Your medical insurance may pay for such treatment, but you may ultimately be billed for payment.

Ask the study doctor for more information about this. We also encourage you to determine your health insurer's policy about paying for treatment in a research study.

By signing this consent form, you are not giving up any legal rights.

[INSERT INSTITUTIONAL LANGUAGE HERE]

Contact Information

Contact [Study Contact Name] at [Phone Number(s)] for any of the following reasons:

- if you have any questions about your participation in this study,
- if at any time you feel you have had a research-related injury, illness or a reaction to the study drug, or
- if you have questions, concerns or complaints about the research.

If you have questions about your rights as a research subject or if you have questions, concerns, input or complaints about the research, you may contact:

Western Institutional Review Board® (WIRB®)
1019 39th Avenue SE Suite 120
Puyallup, Washington 98374-2115
Telephone: 1-800-562-4789 or 360-252-2500
E-mail: Help@wirb.com

WIRB is a group of people who perform independent review of research.

WIRB will not be able to answer some study-specific questions, such as questions about appointment times. However, you may contact WIRB if the research staff cannot be reached or if you wish to talk to someone other than the research staff.

Where can I get more information about Cancer and Clinical Trials?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237)

You may also visit the NCI Web site 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 form. You will be given a copy of the protocol (full study plan) upon request. If you want more information about this study, ask your study doctor.

Statement of Consent

I have been given and have read the information in this consent form (or it has been read to me).

All of my/my child's questions about the study and my/my child's participation in it have been answered. Should I/my child have any further questions about the research, I may contact the person conducting the study at the address and telephone number given below:

[Study Contact Name]
[Address]
[City, State Zip code]
[Phone Number(s)]

My/my child's participation is voluntary and I/my child may refuse to participate or withdraw at any time without penalty or prejudice to my/my child's present and/or future care.

I agree to participate/allow my child to participate in this study and I understand that I will receive a signed copy of this form.

I authorize the release of my/my child's medical information for research or regulatory purposes to the sponsor, The Neuroblastoma and Medulloblastoma Translational Research Consortium, Spectrum Health Hospitals and its affiliates, KC Pharma and its affiliates, the FDA, other federal (U.S.) agencies, governmental agencies in other countries, and WIRB®.

Consent and Assent Instructions:

Consent: Subjects 18 years and older must sign on the subject line below
For subjects under 18, consent is provided by the parent or guardian
Assent: Is not required for subjects 12 years and younger
Verbal assent is required for subjects ages 13 through 17 years using the Assent section below

Signature of Subject (18 years and older) Date

Name of Subject Printed

Signature of Parent or Guardian Date
(applicable for children)

(*If available)*

Name of Parent or Guardian Printed

Signature of Parent or Guardian Date
(applicable for children)

Name of Parent or Guardian Printed

ASSENT SECTION:

Statement of person conducting assent discussion:

- I have explained all aspects of the research to the subject to the best of his or her ability to understand.
- I have answered all the questions of the subject relating to this research.
- The subject agrees to be in the research.
- I believe the subject's decision to enroll is voluntary.
- The study doctor and study staff agree to respect the subject's physical or emotional dissent at any time during this research when that dissent pertains to anything being done solely for the purpose of this research.

_____

Signature of Person Conducting Assent Discussion Date

Statement of Parent or Guardian:

My child appears to understand the research to the best of his or her ability and has agreed to participate.

_____

Signature of Parent or Guardian Date

---------- Use this witness section only if applicable ----------

If this consent form is read to the subject because the subject or the subject's parent or guardian is unable to read the form, an impartial witness not affiliated with the research or investigator must be present for the consent and sign the following statement:

I confirm that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's parent or guardian. The subject or the subject's parent or guardian freely consented to be in the research study.

_____

Signature of Impartial Witness Date

Note: This signature block cannot be used for translations into another language. A translated consent form is necessary for enrolling subjects who do not speak English.

HIPAA AUTHORIZATION FORM FOR USE & DISCLOSURE OF HEALTH INFORMATION FOR RESEARCH PURPOSES (TEMPLATE)

The information we are asking to use and disclose (share) for this research study may include your Protected Health Information (PHI). This information is protected by a federal law called 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?

Each subject in this trial will be identified by a unique identifier that will be used on all report forms and any other material submitted to the NMTRC. Report Forms for this study will be both paper and electronic. Electronic data will be stored in a secure data center. Your health information will be collected and entered in this password-secure database along with the information from other people taking part in this study, and will only be accessible to the people involved in conducting this research.

Why am I being asked to give permission for the use and disclosure of my information?

Your health information will be used to evaluate the safety and tolerability of the study drug, DFMO, in combination with another drug (bortezomib) as well as your tumor's response to the study drug.

To evaluate the study drug and your response, we need to see and use your health information.

What information will be used and shared for this study?

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

- Your date of birth, name, contact information, medical record number, and insurance information.
- Existing medical records and medical history.
- New health information collected for purposes of this study.
- Copies of medical records you have with other health care providers.

With whom will my information be shared (disclosed)?

- The Sponsor(s) of the research or its agents (monitors, auditors): Dr. Giselle Sholler, the Neuroblastoma and Medulloblastoma Translational Research Consortium (NMTRC), affiliates of the NMTRC, and the NMTRC010B study committee
- The study doctor and his/her research staff
- Spectrum Health Hospitals staff or its agents
- KC Pharma (the maker of the study drug)
- The Western Institutional Review Board® (WIRB®)
- The Spectrum Health Institutional Review Board (IRB) and its staff
- The Food and Drug Administration (FDA) and other government agencies who regulate this study

Once your protected health information has been shared (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 your treating institution. 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 and shared?

This authorization has no expiration date.

Can I stop my protected health information from being collected and shared?

You can tell us to stop collecting your health information at any time. We will stop using and sharing your information, 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 using and sharing your health information, you must tell us in writing. Send your written request to:

[insert study doctor contact information]

What happens if I do not want you to use and share my health information?

If you decide not to give permission for us to use and share your health information, you will not be able to participate in this study. Your decision will in no way affect your medical care or cause you to lose any benefits to which you are entitled.

When will my information be destroyed?

We do not know when your information will no longer be used. Unless you tell us to stop using and sharing your information, it will be kept for an indefinite length of time.

[If the HIPAA authorization form will be a document separate from the consent form, appropriate signatures blocks need to be inserted here].

ADDITIONAL OPTIONAL TUMOR BIOLOGY CONSENT

There are optional biology tests that you may agree to participate in if you wish. These include urine and blood samples, extra bone marrow samples, and extra tumor samples. These samples may be collected during routine procedures while you are in the study, and will be used for research tests and studies that will not directly impact your treatment. These research tests and studies may benefit future children with neuroblastoma or other tumors.

If you agree to allow your samples to be used for these future research tests, your samples will be stored in a safe and confidential laboratory area indefinitely. Neither your name nor any other information that identifies you will be used to identify your sample

when they are stored in the lab. The samples will be identified only by a unique, de-identified code. Samples will be frozen and stored in a carefully controlled deep freezer. The samples that are stored for future research may only be used by Dr. Sholler and the other investigators who are participating in this study or other NMTRC studies. No information that identifies you will be used for any of these future research tests and studies.

You have the option to remove the samples from the laboratory at any time. In the 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.

There is no way to predict exactly what research tests will be performed with the stored samples. 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 primary treating oncologist about what the research test results might mean. Only your primary treating oncologist will be notified and the information will not become part of your medical record. Your primary treating oncologist 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 primary treating oncologist may decide that no action is needed.

Future research tests will be looking at genetic information collected from the samples you provide. A Federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways: Health insurance companies and group health plans may not request your genetic information that we get from this research. Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums. Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

GINA <u>does not</u> protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. GINA <u>does not</u> prohibit discrimination on the basis of an already manifest genetic disease or disorder.

1. I agree that additional <u>urine samples</u> may be taken and sent to a laboratory working with the NMTRC for additional tests.

   #1: Yes_____ No_____ _____ / _____
   Initials Date

2. I agree that additional <u>blood samples</u> may be taken and sent to a laboratory working with the NMTRC for additional tests.

#2: Yes_____ No_____ _____ / _____
Initials Date

3. I agree that additional <u>blood samples</u> may be taken and sent to an NMTRC laboratory for biological correlates and additional studies.

#3: Yes_____ No_____ _____ / _____
Initials Date

4. I agree that extra <u>bone marrow</u> may be taken and sent to an NMTRC laboratory for additional studies.

#4: Yes_____ No_____ _____ / _____
Initials Date

5. If I have a standard of care tumor extraction, <u>extra tumor samples</u> may be taken and sent to an NMTRC laboratory for additional studies.

#5: Yes_____ No_____ _____ / _____
Initials Date

6. I agree to let researchers store material (e.g., leftover urine, blood, cells or genetic material that is taken at the time of a procedure) for future use to learn about, prevent, or treat cancer.

#6: Yes_____ No_____ _____ / _____
Initials Date

Attestation Statement

I confirm that the research study was thoroughly explained to the subject or the subject's parent or guardian. I reviewed the consent form with the subject and answered the subject's or the subject's parent or guardian questions. The subject or the subject's parent or guardian appeared to have understood the information and was able to answer the following questions correctly:

1. What is the purpose of this study?
2. If you decide to be in the study, what will you be asked to do?
3. What is the possible benefit of participating in this study?
4. What are the possible risks of participating in this study?
5. If you decide not to participate in this study, what options do you have?
6. Will participating in this study cost you anything? If so, what will you have to pay for?
7. Do you have to be in this study?
8. If you decide to be in the study, can you leave the study when you want to?

_____	_____
Printed Name of Person Conducting the Informed Consent Discussion	Position
_____	_____
Signature of Person Conducting the Informed Consent Discussion	Date