This model informed consent form has been reviewed by the DCT/NCI and is the official consent document for this study. Local IRB changes to this document are allowed. (Institutions should attempt to use sections of this document which are in bold type in their entirety.) Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to the risks or alternatives sections, they must be justified in writing by the investigator and approved by the IRB.

SAMPLE RESEARCH INFORMED CONSENT/PARENTAL PERMISSION FORM

ADVL1823, Larotrectinib (LOXO-101, NSC# 788607, [redacted] for Previously Untreated TRK Fusion Pediatric Solid Tumors and TRK Fusion Relapsed Pediatric Acute Leukemias

(FOR PATIENTS ON PARTS A & B OF THE STUDY ONLY)

If you are a parent or legal guardian of a child who may take part in this study, permission from you is required. The assent (agreement) of your child may also be required. When we say "you" in this consent form, we mean you or your child; "we" means the doctors and other staff.

Why am I being invited to take part in this study?

You are being asked to take part in this research study because you have been diagnosed with a type of cancer that has a mutation called a TRK fusion.

This study is called a clinical trial. A clinical trial is a research study involving treatment of a disease in human patients. This trial is part of the national NCI Clinical Trials Network (NCTN) program which is sponsored by the National Cancer Institute (NCI). The trial will be conducted by the network of NCTN researchers, led by the Children's Oncology Group (COG).

It is common to enroll children and adolescents with cancer in a clinical trial that seeks to improve cancer treatment over time. Clinical trials include only people who choose to take part. You have a choice between another treatment for your cancer and this clinical trial.

Please take your time to make your decision. You may want to discuss it with your friends and family. We encourage parents to include their child in the discussion and decision to the extent that the child is able to understand and take part.

What is the current standard of treatment for this disease?

This study will enroll patients with many different types of cancer. The standard of care treatment for your cancer depends on the specific type of cancer you have. In general, patients with solid tumors are treated with chemotherapy that is given either by mouth, into the vein, or both. In addition, most patients with solid tumors will receive either surgery, radiation therapy, or both to the sites of disease. For some of these cancers, there are specific treatment protocols that have been established. For others, standards of care are not well established. Please ask your doctor for information about your specific cancer and available options.

Why is this study being done?

This is a Phase 2 study of a drug called larotrectinib. Larotrectinib is a drug that has been approved by the US Food and Drug Administration (FDA) for the treatment of children and adults with TRK fusion cancers that have spread after standard therapy, are not able to be surgically removed after standard therapy, or for whom there is no standard therapy available. Using larotrectinib to treat patients with newly diagnosed TRK fusion cancers, as is being done in this study, is still experimental. In a Phase 2 study the goal is to find out what effects, good and/or bad, a drug or combination of drugs has on people with a type of cancer.

Larotrectinib is a type of drug that works by blocking cell signal proteins that are thought to be important for tumors to grow. We are using larotrectinib in this study because it has been shown to block the growth of cancer cells with TRK fusions in test tubes, in animals, and in children and adults that have TRK fusion cancers that have not gone away with or have come back after standard therapy. In children and adults with TRK fusion cancers, larotrectinib has caused tumors to shrink in most but not all patients. This study will evaluate what the effects of larotrectinib are if given at the time cancer is first diagnosed instead of standard therapy. We do not know if it will work against your cancer.

The Phase 1 study of larotrectinib in children with cancer has completed enrollment. The goal of Phase 1 studies is to find a dose of a study drug that can be given without too many side effects. In the Phase 1 study, researchers have determined the dose of larotrectinib to be used in this study that can be given without too many side effects.

The overall goals of this study are to

- **Find out what effects, good and/or bad, larotrectinib has on your type of cancer**
- **To learn more about the side effects of larotrectinib**
- **To learn more about how larotrectinib works against cancer cells**

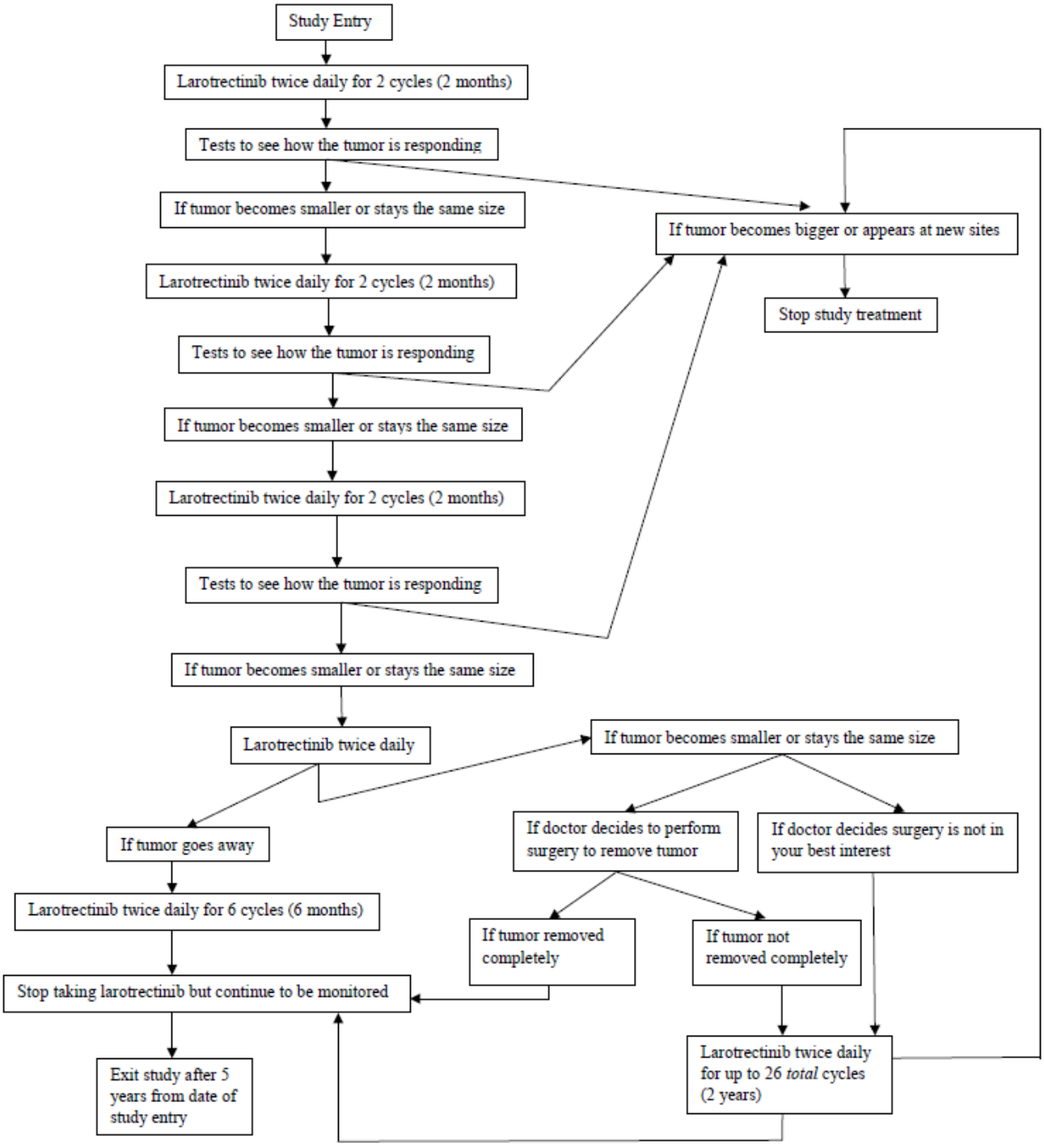
What will happen on this study that is research?

The treatment involves a drug called larotrectinib. The treatment on this study can take up to about 2 years.

In this study you will get larotrectinib twice daily during each cycle. A cycle lasts 28 days (4 weeks). If your cancer goes away from taking larotrectinib you will continue to take larotrectinib twice daily for at least a year total and 6 more cycles (around 6 months) after your cancer went away and then you will stop. Though you will not be taking larotrectinib, you will still be involved in the study and you will continue to be monitored. If your cancer gets better but does not fully go away, your doctor may recommend surgery to remove the rest of your cancer. If the cancer is completely removed from the surgery then you will stop taking larotrectinib but will continue to be monitored. If your cancer is not completely removed from the surgery, or if your doctor decides not to perform surgery at all, then you will continue taking larotrectinib for up to 26 cycles. You will then stop receiving larotrectinib on this study and be monitored. If your cancer ever gets worse or you develop serious side effects during the study, you will stop taking larotrectinib immediately.

Diagram of Treatment

This chart shows the treatments on this study.



Treatment that is Research

Larotrectinib will be given as either a capsule or a liquid. If you are given larotrectinib capsules, the capsules must be swallowed whole through the mouth. If you are given larotrectinib as a liquid, the liquid will either need to be swallowed through the mouth or the liquid will be given to you through a nasogastric or gastrostomy tube.

You should take each dose of larotrectinib approximately 12 hours apart, at about the same time each day. If you vomit after taking a dose, do not retake the dose. Do not eat grapefruit, drink grapefruit juice, or eat Seville oranges while being treated with larotrectinib.

The table below describes one cycle of study therapy

Drug	How the drug will be given	Days
Larotrectinib	By mouth/through a nasogastric or gastrostomy tube	Twice daily for 28 days

During treatment the cancer will be evaluated with imaging scans following Cycles 2, 4, 6, 9, 12, 16, 20, and 24. If you complete the planned treatment with larotrectinib, your cancer will continue to be monitored with imaging scans 3, 6, 12, 18, 24, 30, 36, and 48 months after you complete treatment.

You will be given a Patient Medication Diary at the beginning of each cycle of larotrectinib. Use the diary to record the date and time you take the drug, the strength of each capsule or the volume of the liquid, side effects you experience, and any other medications you are taking. The diary should be returned to the clinic before starting the next cycle. This will help us to know how much of the drug you take and how it made you feel.

Research Study Tests and Procedures

A number of tests will be performed that are part of regular cancer care and may be done even if you do not take part in this study. A partial list is provided below under "Standard Tests and Procedures".

Some copies of the scans used to diagnose the cancer and to evaluate the response to therapy will be sent to a central review center as part of COG quality control. The results of these reviews will not be returned to you.

Standard Tests and Procedures

- Frequent labs to monitor your blood counts and blood chemistries
- Urine tests to measure how your kidneys are functioning
- Pregnancy test for females of childbearing age before treatment begins and prior to each cycle
- X-rays and imaging scans to monitor your response to treatment

Research Study Tests

The following tests will be done because you are part of this study. If you were not in the study you would probably not have these tests.

Neuropsychological and Quality of Life Tests (Required)

You will be asked to complete neuropsychological and quality of life tests to monitor how your brain functions and to see if the treatment has an effect on how your brain functions.

Archived Tumor Tissue Studies (Required)
When you were diagnosed with a TRK fusion cancer, your doctor removed some of your tumor tissue. We would like to keep some of this tissue that is left over and look at the types of cells, proteins, and mutations that can be found in the tissue. The information learned would not change the way you are treated, and the results of these tests will not be returned to you. The tissue will be sent directly to the lab for testing and will not be sold.

If you end up having surgery to remove your tumor on this study, we would also like to keep some of that tissue. If your cancer is in your bone marrow, we would also like to keep some of the tissue that is removed when you have your bone marrow evaluations.

Circulating Tumor DNA Studies (Optional)
We would also like to collect blood samples (5-20 mL or 1-4 teaspoons each [depending on your weight]) to see if a blood test can show whether or not the tumor DNA has changed from when the tumor was biopsied. If you choose to take part, blood samples will be collected before you start taking larotrectinib in Cycle 1, before your morning larotrectinib dose on Cycle 1, Day 15, before your morning larotrectinib dose on Cycle 2, Day 1, before Cycle 7, and when you complete treatment with larotrectinib. If your tumor ever gets worse while you are in this study, we would also like to collect a blood sample then.

You can still be a part of the main study even if you say "No" to taking part in this optional research study. Please indicate by initialing below whether you choose to participate in the circulating tumor DNA studies.

_____/_____ Yes, I agree to participate in the circulating tumor DNA studies.

_____/_____ No, I do not agree to participate in the circulating tumor DNA studies.

Additional Tumor Tissue Studies (Optional)
If your tumor ends up getting worse while you are on this study and your doctor performs tests or surgery on your tumor tissue, we would like to keep some of this tissue to see if the tumor tissue cells, proteins, or mutations changed from when you were originally diagnosed. You can still be a part of the main study even if you say "No" to taking part in this optional research study. Please indicate by initialing below whether you choose to participate in this study in the event that your tumor gets worse.

_____/_____ Yes, I agree to participate in the additional tumor tissue studies.

_____/_____ No, I do not agree to participate in the additional tumor tissue studies.

Specimens for optional research tests

The choice to let us use specimens for research is up to you. No matter what you decide to do, it will not affect your care. You can still be a part of the main study even if you say 'No' to taking part in any of these optional research studies.

If you decide now that your specimens can be used for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your specimens. Then, any specimens that we have will be destroyed.

What side effects or risks can I expect from being in the study?

Treatment Risks
All people who receive cancer treatment are at risk of having side effects.

The risks of taking larotrectinib are listed below.

Risks of Study
If you agree to participate in this study and there is already a standard treatment for your cancer (see page 1), you may receive the standard treatment for your cancer later than you would have if you had not participated in this study.

If you choose to take part in this study, there is a risk that the larotrectinib may not be as good as the usual approach for your cancer or condition at shrinking or stabilizing your cancer.

You also may have the following discomforts:

- Spend more time in the hospital or doctor's office.
- Be asked sensitive or private questions about things which you normally do not discuss.
- May not be able to take part in future studies.

[redacted]

There is also a risk that you could have side effects from the study drugs/study approach.

Here are important things to know about side effects:

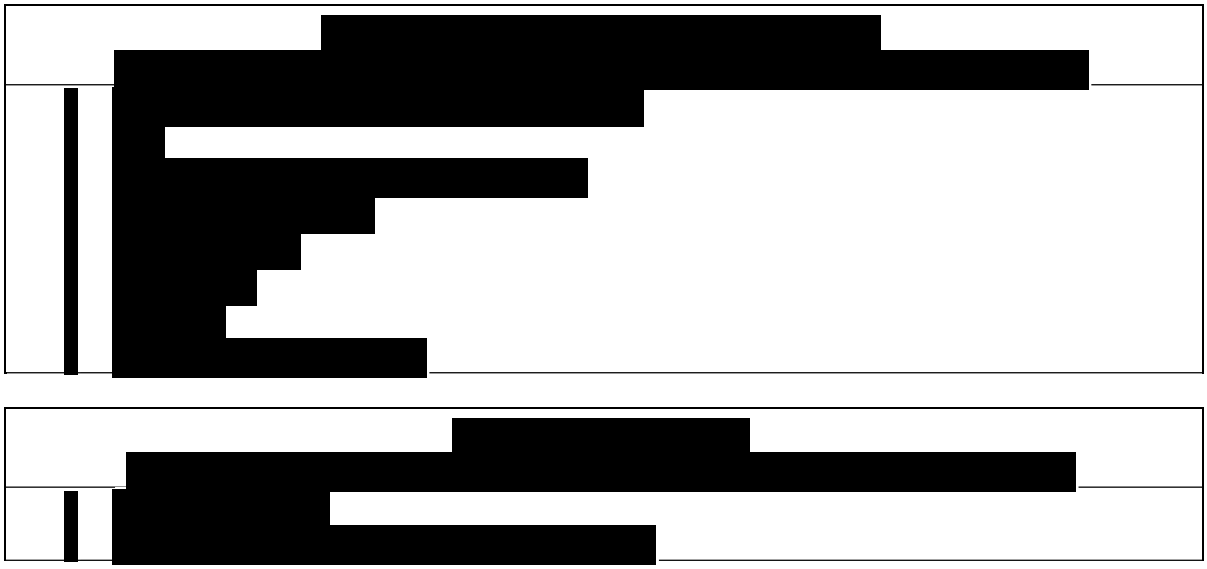
- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may make it hard for you to have children.
- Some side effects may be mild. Other side effects may be very serious and even result in death.

You can ask your study doctor questions about side effects at any time. Here are important ways to make side effects less of a problem:

- If you notice or feel anything different, tell your study doctor. He or she can check to see if it is a side effect.
- Your study doctor will work with you to treat your side effects.
- Your study doctor may adjust the study drugs to try to reduce side effects.

The tables below show the most common and the most serious side effects doctors know about. There might be other side effects doctors do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

[redacted]



[redacted]

Reproductive risks

Women should not become pregnant and men should not father a baby while on this study because larotrectinib can be harmful for an unborn baby. If you or your partner can get pregnant, it is important for you to use birth control or not have sex while on this study and for at least one month after your final dose of larotrectinib. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some birth control methods might not be approved for use in this study. If you are a woman and become pregnant or suspect you are pregnant while participating in this study, please inform your treating physician immediately. Women should not breastfeed a baby while on this study and for 3 days following their final dose of larotrectinib. Also check with your doctor about how long you should not breastfeed after you stop the study treatment(s).

Are there benefits to taking part in the study?

The potential benefit of the treatment with larotrectinib is that it may cause your cancer to shrink or go away. Because there is not much information about the effect of larotrectinib in patients with newly diagnosed cancers, we do not know if you will benefit from taking part in this study. Information learned from this study may help future patients with cancer.

What other options are there?

Instead of being in this study, you have these options:

- **Getting treatment for your cancer without being in a study. These treatments vary depending on the type of cancer you have.**
- **Taking part in another study.**

Please talk to your doctor about these and other options.

How many people will take part in the study?

The total number of people enrolled on this study is expected to be between 9 and 70.

How long is the study?

People in this clinical trial are expected to receive treatment on this study for up to about 2 years. We would like to continue to find out about your health every year for about 5 years after you enter this study. By keeping in touch with you for a while after you complete treatment, we can better understand the long-term effects of the study treatments.

You can stop taking part in the study at any time. However, if you decide to stop participating in the study, we encourage you to talk to the study doctor and your regular doctor first. They will help you stop safely.

Your doctor or the study doctor may decide to take you off this study:
- if he/she believes that it is in your best interest
- if your disease comes back during treatment
- if you experience side effects from the treatment that are considered too severe
- if new information becomes available that shows that another treatment would be better for you
- if you become pregnant

What about privacy?

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.

The Children's Oncology Group 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 in Attachment 1.

Organizations that may look at and/or copy your research or medical records for research, quality assurance and data analysis include groups such as:

- **Children's Oncology Group**

- **Representatives of the National Cancer Institute (NCI), Food and Drug Administration (FDA), and other U.S. and international governmental regulatory agencies involved in overseeing research**
- **The Institutional Review Board of this hospital**
- **Pediatric Central Institutional Review Board (CIRB) of the National Cancer Institute**
- **Any drug company supporting the study or their designated reviewers.**

What are the costs?

Taking part in this study may lead to added costs to you or your insurance company. There are no plans for the study to pay for medical treatment. Please ask about any expected added costs or insurance problems. Staff will be able to assist you with this.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury. However by signing this form, you are not giving up any legal rights to seek to obtain compensation for injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization.

The drug company that makes larotrectinib is supplying the drug at no charge for this study. The drug company does not cover the cost of getting the larotrectinib ready and giving it to you, so you or your insurance company may have to pay for this.

You will not be charged for the costs of the special blood tests and tumor tissue tests that are being done for research purposes only (see "Research Study Tests").

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://www.cancer.gov/clinicaltrials/learningabout.

Funding support

If you choose to enroll on this study, this institution will receive some money from the Children's Oncology Group to do the research. There are no plans to pay you for taking part in this study.

The drug company that makes larotrectinib is providing money to the Children's Oncology Group to do the research.

This study includes providing specimens to the researcher. There are no plans for you to profit from any new product developed from research done on your specimens.

What are my rights as a participant?

Taking part in this study is voluntary. You may choose not to be in this study. If you decide not to be in this study, you will not be penalized and you will not lose any benefits to which you are entitled. You will still receive medical care.

You can decide to stop being in the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled. Your doctor will still take care of you.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study. A committee outside of COG closely monitors study reports and notifies COG if changes must be made to the study. Members of COG meet twice a year to discuss results of treatment and to plan new treatments.

During your follow-up visits after treatment, you may ask to be given a summary of the study results, which will only be available after the study is fully completed. *A summary of the study results will also be posted on the Children's Oncology Group website (http://www.childrensoncologygroup.org/).* To receive the results, you may either (1) go to the COG website to check if results are available or (2) register your information with the COG on its web site and have an email sent to you when the results are available. Your pediatric oncology team from your hospital can give you additional instructions on how to do this. Please note, that the summary of results may not be available until several years after treatment for all people on the study is completed, and not only when you complete treatment.

Whom do I call if I have questions or problems?

For questions about the study or if you have a research related problem or if you think you have been injured in this study, you may contact Dr. *XXXX* or your doctor at *XXXX*.

If you have any questions about your rights as a research participant or any problems that you feel you cannot discuss with the investigators, you may call *XXXX* IRB Administrator at *XXXX*.

If you have any questions or concerns that you feel you would like to discuss with someone who is not on the research team, you may also call the Patient Advocate at *XXXX*.

Where can I get more information?

The COG Family Handbook for Children with Cancer has information about specific cancers, tests, treatment side effects and their management, adjusting to cancer, and resources. Your doctor can get you this Handbook, or you can get it at https://www.childrensoncologygroup.org/index.php/cog-family-handbook.

Visit the NCI's Web site at http://www.cancer.gov.

If you are in the United States, you may call the NCI's *Cancer Information Service* at: 1-800-4-CANCER (1-800-422-6237).

Information about long term follow-up after cancer treatment can be found at: http://www.survivorshipguidelines.org/.

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.

You will get a copy of this form. You may also ask for a copy of the protocol (full study plan).

Signature

I have been given a copy of all ____ pages of this form. The form includes one (1) attachment.

I have reviewed the information and have had my questions answered.
I agree to take part in this study.

Participant_____Date _____

Parent/Guardian_____Date _____

Parent/Guardian_____Date _____

Physician/PNP obtaining consent_____Date _____

Attachment 1

Certificate of Confidentiality

The Children's Oncology Group 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.

This model informed consent form has been reviewed by the DCT/NCI and is the official consent document for this study. Local IRB changes to this document are allowed. (Institutions should attempt to use sections of this document which are in bold type in their entirety.) Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to the risks or alternatives sections, they must be justified in writing by the investigator and approved by the IRB.

SAMPLE RESEARCH INFORMED CONSENT/PARENTAL PERMISSION FORM

ADVL1823, Larotrectinib (LOXO-101, NSC# 788607, [redacted] for Previously Untreated TRK Fusion Pediatric Solid Tumors and TRK Fusion Relapsed Pediatric Acute Leukemias

(FOR PATIENTS ON PART C OF THE STUDY ONLY)

If you are a parent or legal guardian of a child who may take part in this study, permission from you is required. The assent (agreement) of your child may also be required. When we say "you" in this consent form, we mean you or your child; "we" means the doctors and other staff.

Why am I being invited to take part in this study?

You are being asked to take part in this research study because you have been diagnosed with leukemia that has a mutation called a TRK fusion. Your leukemia has continued to grow (is refractory), or has come back (recurred) during or after treatment with standard therapy.

This study is called a clinical trial. A clinical trial is a research study involving treatment of a disease in human patients. This trial is part of the national NCI Clinical Trials Network (NCTN) program which is sponsored by the National Cancer Institute (NCI). The trial will be conducted by the network of NCTN researchers, led by the Children's Oncology Group (COG).

It is common to enroll children and adolescents with cancer in a clinical trial that seeks to improve cancer treatment over time. Clinical trials include only people who choose to take part. You have a choice between another treatment for leukemia and this clinical trial.

Please take your time to make your decision. You may want to discuss it with your friends and family. We encourage parents to include their child in the discussion and decision to the extent that the child is able to understand and take part.

What is the current standard of treatment for this disease?

When leukemia comes back (recurs) or does not respond to therapy (is refractory), your doctor may recommend other anti-cancer drugs (chemotherapy), cellular therapy (CAR T-cells), radiation therapy, or a bone marrow transplant. For certain cancers, a combination of one or more of these approaches is considered standard treatment. However, for other cancers for which standard therapy is no longer working, the best treatment is not known.

Standards of care for TRK fusion leukemias are generally not well established. Please ask your doctor for information about your specific cancer and available options.

Why is this study being done?

This is a Phase 2 study of a drug called larotrectinib. Larotrectinib is a drug that has been approved by the US Food and Drug Administration (FDA) for the treatment of children and adults with TRK fusion solid cancers that have spread after standard therapy, are not able to be surgically removed after standard therapy, or for whom there is no standard therapy available. Using larotrectinib to treat patients with leukemia is experimental. In a Phase 2 study, the goal is to find out what effects, good and/or bad, a drug or combination of drugs has on people with a type of cancer.

Larotrectinib is a type of drug that works by blocking cell signal proteins that are thought to be important for tumors to grow. We are using larotrectinib in this study because it has been shown to block the growth of cancer cells with mutations in the TRK pathway in test tubes, in animals, and in children and adults that have TRK fusion cancers (solid tumors) that have not gone away with or have come back after standard therapy. In children and adults with TRK fusion solid tumors, larotrectinib has caused tumors to shrink in most but not all patients. Larotrectinib has never been studied in patients with leukemia, and we do not know if it will work against TRK fusion leukemia.

The Phase 1 study of larotrectinib in children with cancer is ongoing. The goal of Phase 1 studies is to find the highest dose of a study drug that can be given without too many side effects. In the Phase 1 study, researchers have determined the dose of larotrectinib to be used in this study that can be given without too many side effects.

The overall goals of this study are to

- **Find out what effects, good and/or bad, larotrectinib has on your type of cancer**
- **To learn more about the side effects of larotrectinib**
- **To learn more about how larotrectinib works against cancer cells**

What will happen on this study that is research?

The treatment involves a drug called larotrectinib. The treatment on this study can take up to about 2 years.

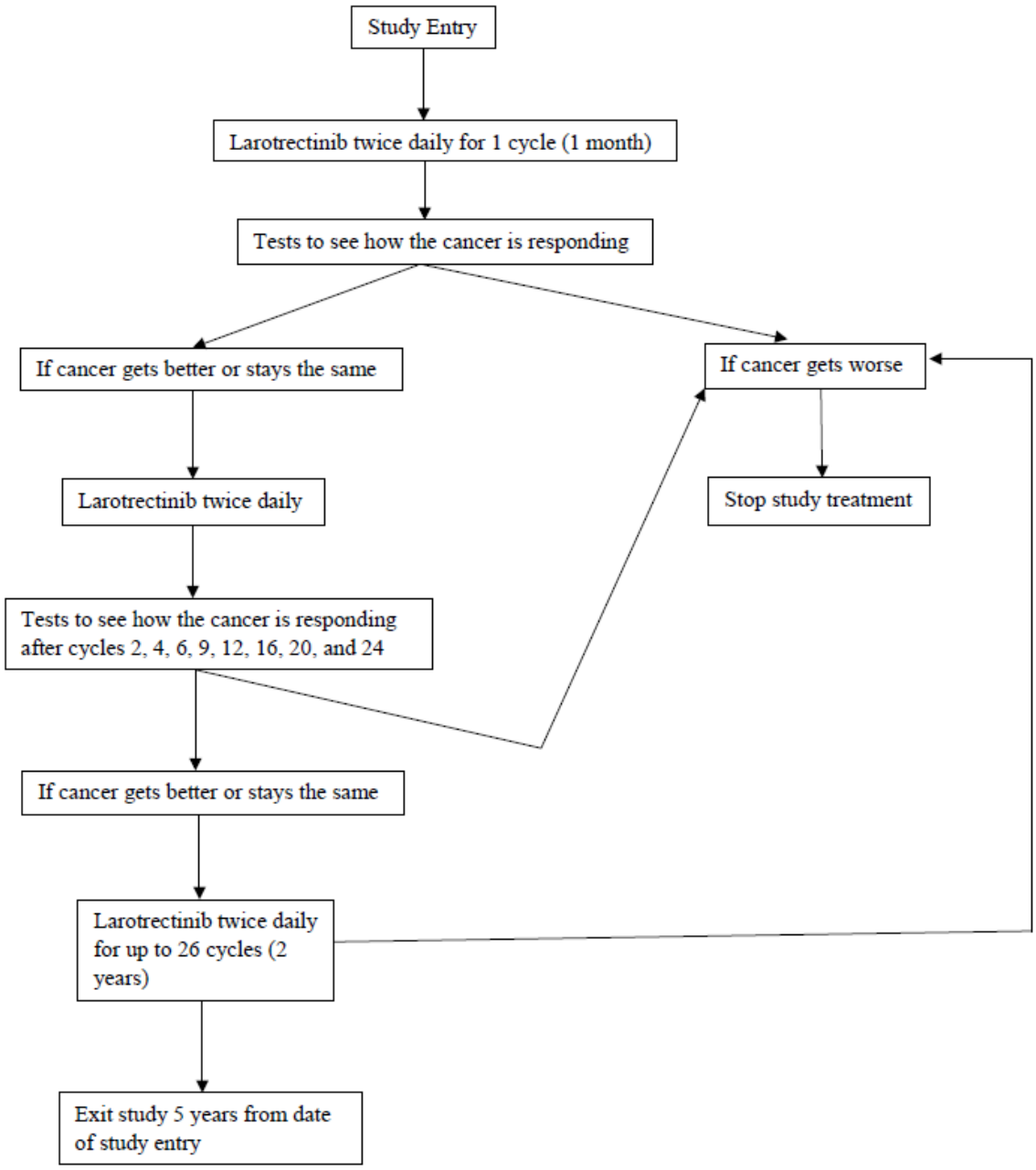
In this study you will get larotrectinib twice daily during each cycle. A cycle lasts 28 days (4 weeks). You may continue to receive larotrectinib for up to 2 years unless you develop serious side effects or your cancer worsens.

Patients may also receive drug(s) through the spinal canal before the beginning of each cycle. These drugs will only be administered once for each cycle. These drugs are all commercial drugs and you will either be given methotrexate, cytarabine, or intrathecal triples (methotrexate + hydrocortisone + cytarabine) depending on the type of leukemia you have and how much leukemia is in your spinal fluid. Your doctor will decide if you should receive these drugs prior to each cycle of therapy.

Certain patients will also receive methotrexate, cytarabine, or intrathecal triples through the spinal cord on days 8, 15, and 22 during cycle 1 only. This will happen to patients whose leukemia has affected their spinal fluid. Your doctor will let you know if you are one of these patients.

Diagram of Treatment

This chart shows the treatments on this study.



Treatment that is Research

Larotrectinib will be given as either a capsule or a liquid. If you are given larotrectinib capsules, the capsules must be swallowed whole through the mouth. If you are given larotrectinib as a liquid, the liquid will either need to be swallowed through the mouth or the liquid will be given to you through a nasogastric or gastrostomy tube.

You should take each dose of larotrectinib approximately 12 hours apart, at about the same time each day. If you vomit after taking a dose, do not retake the dose. Do not eat grapefruit, drink grapefruit juice, or eat Seville oranges while being treated with larotrectinib.

The table below describes one cycle of study therapy

Drug	How the drug will be given	Days	Notes
Methotrexate OR Cytarabine OR	Into the spinal fluid	Before each cycle.	Your doctor will decide if you should receive these drugs or not.
Methotrexate + Hydrocortisone + Cytarabine		One time on days 8, 15, and 22 (**during cycle 1 only**)	The doses on days 8, 15, and 22 during cycle 1 are only for patients whose leukemia has affected their spinal fluid. Your doctor will let you know if you are one of these patients.
Larotrectinib	By mouth/through a nasogastric or gastrostomy tube	Twice daily for 28 days	All patients will receive this drug.

During treatment the cancer will be evaluated with bone marrow evaluations/biopsies following Cycles 1, 2, 4, 6, 9, 12, 16, 20, and 24.

You will be given a Patient Medication Diary at the beginning of each cycle of larotrectinib. Use the diary to record the date and time you take the drug, the strength of each capsule or the volume of the liquid, side effects you experience, and any other medications you are taking. The diary should be returned to the clinic before starting the next cycle. This will help us to know how much of the drug you take and how it made you feel.

Research Study Tests and Procedures

A number of tests will be performed that are part of regular cancer care and may be done even if you do not take part in this study. A partial list is provided below under “Standard Tests and Procedures”.

Some copies of the tests used to diagnose the cancer and to evaluate the response to therapy will be sent to a central review center as part of COG quality control. The results of these reviews will not be returned to you.

Standard Tests and Procedures

- Frequent labs to monitor your blood counts and blood chemistries
- Urine tests to measure how your kidneys are functioning
- Pregnancy test for females of childbearing age before treatment begins and prior to each cycle
- Bone marrow evaluations, lumbar punctures, and for some patients X-rays and imaging scans to monitor your response to treatment

Research Study Tests

The following tests will be done because you are part of this study. If you were not in the study you would probably not have these tests.

Neuropsychological and Quality of Life Tests (Required)
You will be asked to complete neuropsychological and quality of life tests to monitor how your brain functions and to see if the treatment has an effect on how your brain functions.

Cerebrospinal Fluid and Blood Pharmacokinetics (Required)
We would also like to collect blood samples (3 mL or 1/2 teaspoon each) and samples of your spinal fluid (0.5 mL or 1/10 teaspoon each) at the end of cycle 1 during the lumbar puncture that will be performed to assess your response to treatment. If you are a patient who receives methotrexate, cytarabine, or intrathecal triples on days 8, 15, and 22 of cycle 1, we would also like to collect blood samples then. These samples would help us see how much larotrectinib gets through to your brain.

A maximum blood volume of 12 mL (about 2 ½ teaspoons) and a maximum spinal fluid volume of 2 mL (about ½ teaspoon) will be drawn for the cerebrospinal fluid and blood pharmacokinetic studies. *This amount of blood and spinal fluid is safe to draw even from small children.*

Archived Tumor Tissue Studies (Required)
When you were diagnosed with TRK fusion leukemia, your doctor removed some of your bone marrow and blood. We would like to keep some of the samples that are left over and look at the types of cells, blood vessels, and proteins that can be found in the bone marrow and blood. The information learned would not change the way you are treated, and the results of these tests will not be returned to you. The tissue will be sent directly to the lab for testing and will not be sold.

We would also like to keep some of the bone marrow that is removed when you have your bone marrow evaluations.

Circulating Tumor DNA Studies (Optional)
We would also like to collect blood samples (5-20 mL or 1-4 teaspoons each [depending on your weight]) to see if a blood test can show whether or not the cancer DNA has changed from when the cancer was biopsied. If you choose to take part, blood samples will be collected before you start taking larotrectinib in Cycle 1, before your morning larotrectinib dose on Cycle 1, Day 15, before your morning larotrectinib dose on Cycle 2, Day 1, before Cycle 7, and at the end of study treatment. If your cancer ever gets worse while you are in this study, we would also like to collect blood samples then.

You can still be a part of the main study even if you say "No" to taking part in this optional research study. Please indicate by initialing below whether you choose to participate in the circulating tumor DNA studies.

_____/_____ Yes, I agree to participate in the circulating tumor DNA studies.

_____/_____ No, I do not agree to participate in the circulating tumor DNA studies.

Specimens for optional research tests

The choice to let us use specimens for research is up to you. No matter what you decide to do, it will not affect your care. You can still be a part of the main study even if you say 'No' to taking part in any of these optional research studies.

If you decide now that your specimens can be used for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your specimens. Then, any specimens that we have will be destroyed.

What side effects or risks can I expect from being in the study?

Treatment Risks
All people who receive cancer treatment are at risk of having side effects.

The risks of taking each of the medications in this study are listed below.

Risks of Study
If you choose to take part in this study, there is a risk that the larotrectinib may not be as good as the usual approach for your cancer or condition at shrinking or stabilizing your cancer.

You also may have the following discomforts:

- Spend more time in the hospital or doctor's office.
- Be asked sensitive or private questions about things you normally do not discuss.
- May not be able to take part in future studies.

[redacted]

There is also a risk that you could have side effects from the study drugs/study approach.

Here are important things to know about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may make it hard for you to have children.
- Some side effects may be mild. Other side effects may be very serious and even result in death.

You can ask your study doctor questions about side effects at any time. Here are important ways to make side effects less of a problem:

- If you notice or feel anything different, tell your study doctor. He or she can check to see if it is a side effect.
- Your study doctor will work with you to treat your side effects.
- Your study doctor may adjust the study drugs to try to reduce side effects.

The tables below show the most common and the most serious side effects doctors know about. Keep in mind that there might be other side effects doctors do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

[redacted]

[redacted]

Possible Side Effects of Methotrexate when given into the spinal fluid (intrathecal):

COMMON, SOME MAY BE SERIOUS In 100 people receiving methotrexate when given into the spinal fluid, more than 20 and up to 100 may have:
• **Nausea** • **Headache**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving methotrexate when given into the spinal fluid, from 4 to 20 may have:
• **Swelling of the brain which may cause blurred vision, and/or confusion** • **Damage to the brain which may cause changes in thinking** • **Confusion, dizziness** • **Vomiting** • **Rash** • **Tiredness** • **Pain** • **Anemia which may require blood transfusions** • **Infection, especially when white blood cell count is low** • **Bruising, bleeding** • **Difficulty with speaking**

RARE, AND SERIOUS In 100 people receiving methotrexate when given into the spinal fluid, 3 or fewer may have:
• **Seizure** • **Damage to the brain which could lead to coma** • **Paralysis, weakness** • **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat** • **Bleeding into the space of the spine at the site of the injection**

Risks and side effects related to cytarabine when given into the spinal fluid (intrathecal):

COMMON, SOME MAY BE SERIOUS In 100 people receiving cytarabine (ara-c) when given into the spinal fluid, more than 20 and up to 100 may have:
• **Nausea, vomiting** • **Fever** • **Headache**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving cytarabine (ara-c) when given into the spinal fluid, from 4 to 20 may have:
• **Anemia which may cause tiredness, or may require blood transfusions** • **Infection, especially when white blood cell count is low** • **Bruising, bleeding** • **Tiredness, dizziness, loss of coordination** • **Numbness and tingling of the arms and legs** • **Inflammation of the lining of the brain that can lead to headache, numbness and tingling**

RARE, AND SERIOUS In 100 people receiving cytarabine (ara-c) when given into the spinal fluid, 3 or fewer may have:
• **Seizure** • **Paralysis** • **Blurred vision with a chance of blindness** • **Damage to the brain that may result in a decrease in the ability to learn**

Possible Side Effects of Intrathecal Triples (cytarabine, methotrexate, and hydrocortisone) when given into the spinal fluid:

COMMON, SOME MAY BE SERIOUS In 100 people receiving intrathecal triples, more than 20 and up to 100 may have:
• **Nausea, vomiting** • **Fever** • **Headache**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving intrathecal triples, from 4 to 20 may have:
• **Swelling of the brain which may cause blurred vision and/or confusion** • **Damage to the brain which may cause changes in thinking** • **Difficulty with speaking** • **Pain** • **Confusion, dizziness** • **Tiredness** • **Rash**

RARE, AND SERIOUS In 100 people receiving intrathecal triples, 3 or fewer may have:
• **Seizure** • **Damage to the brain which could lead to coma** • **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat** • **Bleeding into the space of the spine at the site of the injection** • **Paralysis, weakness** • **Infection**

<u>Reproductive risks</u>

Women should not become pregnant and men should not father a baby while on this study because larotrectinib can be harmful for an unborn baby. If you or your partner can get pregnant, it is important for you to use birth control or not have sex while on this study and for at least one month after your final dose of larotrectinib. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some birth control methods might not be approved for use in this study. If you are a woman and become pregnant or suspect you are pregnant while participating in this study, please inform your treating physician immediately. Women should not breastfeed a baby while on this study and for 3 days following their final dose of

larotrectinib. Also check with your doctor about how long you should not breastfeed after you stop the study treatment(s).

Are there benefits to taking part in the study?

The potential benefit of the treatment with larotrectinib is that it may cause your leukemic cells to decrease in number or go away. Because there is not much information about the effect of larotrectinib on TRK fusion leukemias, we do not know if you will benefit from taking part in this study. Information learned from this study may help future patients with cancer.

What other options are there?

Instead of being in this study, you have these options:

- **Getting treatment for your cancer without being in a study**
- **Taking part in another study.**
- **Getting comfort care, also called palliative care.** This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly. Instead it tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Please talk to your doctor about these and other options.

How many people will take part in the study?

The total number of people enrolled on this study is expected to be between 9 and 70.

How long is the study?

People in this clinical trial are expected to receive treatment on this study for up to 2 years. We would like to continue to find out about your health every year for about 5 years after you enter this study. By keeping in touch with you for a while after you complete treatment, we can better understand the long-term effects of the study treatments.

You can stop taking part in the study at any time. However, if you decide to stop participating in the study, we encourage you to talk to the study doctor and your regular doctor first. They will help you stop safely.

Your doctor or the study doctor may decide to take you off this study:

- if he/she believes that it is in your best interest
- if your disease comes back during treatment
- if you experience side effects from the treatment that are considered too severe
- if new information becomes available that shows that another treatment would be better for you
- if you become pregnant

What about privacy?

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.

The Children's Oncology Group 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 in Attachment 1.

Organizations that may look at and/or copy your research or medical records for research, quality assurance and data analysis include groups such as:

- **Children's Oncology Group**
- **Representatives of the National Cancer Institute (NCI), Food and Drug Administration (FDA), and other U.S. and international governmental regulatory agencies involved in overseeing research**
- **The Institutional Review Board of this hospital**
- **Pediatric Central Institutional Review Board (CIRB) of the National Cancer Institute**
- **Any drug company supporting the study or their designated reviewers.**

What are the costs?

Taking part in this study may lead to added costs to you or your insurance company. There are no plans for the study to pay for medical treatment. Please ask about any expected added costs or insurance problems. Staff will be able to assist you with this.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury. However by signing this form, you are not giving up any legal rights to seek to obtain compensation for injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization.

The drug company that makes larotrectinib is supplying the drug at no charge for this study. The drug company does not cover the cost of getting the larotrectinib ready and giving it to you, so you or your insurance company may have to pay for this.

You will not be charged for the costs of the special spinal fluid tests, tumor tissue tests, or blood tests that are being done for research purposes only (see "Research Study Tests").

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://www.cancer.gov/clinicaltrials/learningabout.

Funding support

If you choose to enroll on this study, this institution will receive some money from the Children's Oncology Group to do the research. There are no plans to pay you for taking part in this study.

The drug company that makes larotrectinib is providing money to the Children's Oncology Group to do the research.

This study includes providing specimens to the researcher. There are no plans for you to profit from any new product developed from research done on your specimens.

What are my rights as a participant?

Taking part in this study is voluntary. You may choose not to be in this study. If you decide not to be in this study, you will not be penalized and you will not lose any benefits to which you are entitled. You will still receive medical care.

You can decide to stop being in the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled. Your doctor will still take care of you.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study. A committee outside of COG closely monitors study reports and notifies COG if changes must be made to the study. Members of COG meet twice a year to discuss results of treatment and to plan new treatments.

During your follow-up visits after treatment, you may ask to be given a summary of the study results, which will only be available after the study is fully completed. *A summary of the study results will also be posted on the Children's Oncology Group website (http://www.childrensoncologygroup.org/).* To receive the results, you may either (1) go to the COG website to check if results are available or (2) register your information with the COG on its web site and have an email sent to you when the results are available. Your pediatric oncology team from your hospital can give you additional instructions on how to do this. Please note, that the summary of results may not be available until several years after treatment for all people on the study is completed, and not only when you complete treatment.

Whom do I call if I have questions or problems?

For questions about the study or if you have a research related problem or if you think you have been injured in this study, you may contact Dr. *XXXX* or your doctor at *XXXX*.

If you have any questions about your rights as a research participant or any problems that you feel you cannot discuss with the investigators, you may call *XXXX* IRB Administrator at *XXXX*.

If you have any questions or concerns that you feel you would like to discuss with someone who is not on the research team, you may also call the Patient Advocate at *XXXX*.

Where can I get more information?

The COG Family Handbook for Children with Cancer has information about specific cancers, tests, treatment side effects and their management, adjusting to cancer, and resources. Your doctor can get you this Handbook, or you can get it at https://www.childrensoncologygroup.org/index.php/cog-family-handbook.

Visit the NCI's Web site at http://www.cancer.gov.

If you are in the United States, you may call the NCI's *Cancer Information Service* at: 1-800-4-CANCER (1-800-422-6237).

Information about long term follow-up after cancer treatment can be found at: http://www.survivorshipguidelines.org/.

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.

You will get a copy of this form. You may also ask for a copy of the protocol (full study plan).

Signature

I have been given a copy of all ____ pages of this form. The form includes one (1) attachment.

I have reviewed the information and have had my questions answered.
I agree to take part in this study.

Participant_____Date _____

Parent/Guardian_____Date _____

Parent/Guardian_____Date _____

Physician/PNP obtaining consent_____Date _____

Attachment 1

Certificate of Confidentiality

The Children's Oncology Group 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.