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Martha Kruhm, MS, RAC
Head, Protocol and Information Office
Operations and Informatics Branch
Cancer Therapy Evaluation Program
Division of Cancer Treatment and Diagnosis
National Cancer Institute
Executive Plaza North Room 730
Bethesda, MD 20892

Dear Ms. Kruhm,

Enclosed please find Amendment #8A to protocol AALL1731, *A Phase 3 Trial Investigating Blinatumomab (IND#, NSC# 765986) in Combination with Chemotherapy in Patients with Newly Diagnosed Standard Risk or Down syndrome B-Lymphoblastic Leukemia (B-ALL) and the Treatment of Patients with Localized B-Lymphoblastic Lymphoma (B-LLy)*.

Amendment #8A includes administrative corrections to the protocol that were made in response to a clinical information request by the FDA. These changes are noted in the summary of changes table for the protocol below. In addition, an exploratory aim was revised per the recommendation from the CTEP Protocol Information Office (PIO) of the last protocol review for AALL1731.

Additional administrative changes have been made; specific changes are detailed in the Summary of Changes table below. Minor administrative updates (such as the correction of typographical errors, spelling, or updates to the numbers of referenced sections) are tracked in the protocol but not specified.

Please let me know if you have any questions or need additional information.

Sincerely,

Rachel Vasquez, Protocol Coordinator (for)

Sumit Gupta, M.D., AALL1731 Study co-Chair,
Rachel Rau, M.D., AALL1731 Study co-Chair,
John Kairalla, Ph.D., AALL1731 Study Statistician
David Teachey, M.D., Acute Lymphoblastic Leukemia Committee Chair, and
Douglas S. Hawkins, MD, COG Group Chair

A National Cancer Institute-funded group member of the National Clinical Trials Network

SUMMARY OF CHANGES: DS HIGH RISK B-ALL POST-INDUCTION INFORMED CONSENT

In accordance with the above discussion, the following specific revisions have been made to the consent. Additions are in **boldfaced** font and deletions in ~~strikethrough~~ font.

#	Section	Page(s)	Change
1.	General	All	Updated version date of consent to match the current version of the protocol.
2.	Attachment 2	22 23	Updated the risk insert tables for the following agents: • Asparaginase Erwinia chrysanthemi (recombinant) or Asparaginase Erwinia/crisantaspase • Pegaspargase or Calaspargase pegol

This model informed consent form has been reviewed by the DCT/NCI and is the official consent document for this study. Institutions must use the sections of this document that 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 local IRB insists on making deletions or more substantive modifications to any of the sections in bold type, they must be justified in writing by the investigator at the time of the institutional audit.

SAMPLE RESEARCH INFORMED CONSENT/PARENTAL PERMISSION FORM

AALL1731, A Phase 3 Trial Investigating Blinatumomab (IND#, NSC# 765986) in Combination with Chemotherapy in Patients with Newly Diagnosed Standard Risk or Down Syndrome B-Lymphoblastic Leukemia (B-ALL) and the Treatment of Patients with Localized B-Lymphoblastic Lymphoma (B-LLy)

Study title for study participants: A study to compare the addition of Blinatumomab in combination with chemotherapy in patients diagnosed with standard risk B-cell Acute Lymphoblastic Leukemia (B-ALL), Down syndrome B-cell Acute Lymphoblastic Leukemia (B-ALL) and the treatment of patients with localized B-cell Lymphoblastic Lymphoma (B-LLy)

Part II: Post-Induction Therapy for Subjects with Down syndrome and High Risk B-cell Acute Lymphoblastic Leukemia (DS-High B-ALL).

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.

Overview

You are being asked to take part in this research study because you have been diagnosed with **Down Syndrome High Risk B-cell Acute Lymphoblastic Leukemia (DS-High B-ALL).**

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.

The overall goal of this study is to compare the effects, good and/or bad, in replacing some parts of standard chemotherapy with 3 cycles of blinatumomab therapy.

The treatment involves cancer fighting medicines called chemotherapy plus blinatumomab, the investigational drug. The treatment on this part of the study takes about 2 years and is divided into 7 phases.

Another part of this study that is experimental is that the second part (month) of Delayed Intensification therapy is eliminated for all patients and the third cycle of blinatumomab will be given during this time instead.

All people who receive cancer treatment are at risk of having side effects. In addition to killing tumor cells, cancer chemotherapy can damage normal tissue and produce side effects.

Common side effects of chemotherapy include nausea, vomiting, hair loss, and fatigue (tiredness). Drugs may be given to try to prevent or decrease nausea and vomiting. Hair loss is usually temporary but very rarely it may be permanent. Some chemotherapy may make people permanently unable to have children. On rare occasions, people can get a second cancer from chemotherapy. This usually happens years after the chemotherapy is finished. The risks of the individual drugs given as standard treatment are listed in **Attachment 2**.

This study uses the investigational drug blinatumomab. Common side effects of this drug are anemia that may require blood transfusion, diarrhea, nausea, tiredness, fever, bruising, bleeding and headache. A less common but notable side effect is called cytokine release syndrome. Cytokine release syndrome is caused by too much inflammation. The full list of risks for drug blinatumomab are available in the section **What side effects or risks can I expect from being in the study?**

You can ask your study doctor questions about side effects at any time.

We hope that this study will help you personally, but we do not know if it will. The potential benefits to you associated with participation in this study are described in the Section **Are there benefits to taking part in the study?**

You have a choice of deciding to participate in this clinical trial or not. If you do not participate, your doctor will discuss other treatments with you. If you choose to participate, you will receive standard treatment for your leukemia plus the investigational drug blinatumomab. Please take your time to make your decision. You may want to discuss it with your family and friends. 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.

The rest of this form provides detailed information about the study and what to expect should you decide to participate.

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 DS-High B-ALL. The term “risk” refers to the chance of the cancer coming back after treatment. Your leukemia may be considered High Risk because your age at diagnosis was greater than or equal to 10 years old, your initial white blood cell count was high, your minimal residual disease (MRD) level was high at Day 29 of Induction therapy, you have unfavorable genetic characteristics, and/or you may have levels of central nervous system (CNS) disease, and/or disease in the testes (for boys), and/or received steroids before diagnosis. Your leukemia may also be considered High Risk if there are leukemia cells in parts of your body other than the bone marrow at the end of Induction treatment.

B-cell Acute Lymphoblastic Leukemia (B-ALL) is a cancer of the blood cells that occurs in the bone marrow. The bone marrow is the soft tissue in the center of the bones where blood cells are made. B-ALL is a cancer in which young, abnormal, infection-fighting white blood cells

(called blasts) crowd out normal bone marrow cells and spread into the blood stream. Blasts can also spread to the brain, spinal cord, testes, and other organs.

This study is called a clinical trial. A clinical trial is a research study involving treatment of a disease in human patients. This study is organized by Children's Oncology Group (COG). COG is an international research group that conducts clinical trials for children with cancer. More than 200 hospitals in North America, Australia, New Zealand, and Europe are members of 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 a standard treatment for DS-High B-ALL disease and this clinical trial.

Please take your time to make your decision. You may want to discuss it with your family and friends. 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?

Standard therapy is treatment that most cancer doctors would recommend and that you would otherwise receive to treat your leukemia, even if you decide not to participate in a clinical trial. Standard treatment for B-ALL has several phases. In the first phase called Induction (Part I), we try to remove all visible signs of leukemia and allow normal blood cells to be restored. This is called remission. Disease remission is when the leukemia seems to have disappeared, but studies have shown additional therapy is needed to prevent it from coming back. You have already received this portion of therapy.

In the remainder of therapy called post-Induction (Part II), we try to get rid of any remaining leukemia cells to keep the leukemia from coming back. Post-Induction therapy has several phases that are called Consolidation, Interim Maintenance (IM), Delayed Intensification (DI), and Maintenance. During Consolidation, IM, and DI, we try to eliminate any remaining leukemia cells. In the final phase, called Maintenance, we try to keep the leukemia from coming back. All phases of treatment are very important.

Why is this study being done?

In previous COG studies, patients with DS-High B-ALL suffered from infection during treatment. Infections and death are known possible complications of treatment, but more of these complications of treatment occurred in patients with DS than in patients without DS. On this study, Delayed Intensification therapy (described below) has been shortened from the usual treatment in an effort to decrease the risk of infections. In addition, we are testing whether the addition of three cycles of therapy with a drug called blinatumomab will increase the chance of cure in DS-High B-ALL.

Blinatumomab is approved by the Food and Drug Administration (FDA) for the treatment of children in first or second complete remission with MRD greater than or equal to 0.1% and also for the treatment of children with relapsed (cancer comes back) or refractory (cancer doesn't respond to therapy) B-ALL. Blinatumomab is an antibody. Antibodies are large proteins that identify and target foreign substances in the body. Blinatumomab searches for cancer cells and

attaches itself to the cancer cell. Once attached, it engages part of the immune system that can kill the cancer cells. We chose to use blinatumomab in this study because it has shown very good results in getting children with a second or later relapse of B-ALL back into remission. However, the use of blinatumomab in newly diagnosed patients who have not relapsed is experimental on this study. We are hoping that blinatumomab will help lower the chance of relapse.

We do not know if eliminating part of the DI treatment phase and using three cycles of blinatumomab will improve the outcome of DS-High B-ALL patients. That is why we are doing this study.

The overall goal of this study is to compare the effects, good and/or bad, in replacing some parts of standard chemotherapy with 3 cycles of blinatumomab therapy.

What will happen on this study that is research?

Most of the treatment in this study is standard or regular therapy for people with DS-High B-ALL. Treatment that is standard for DS-High B-ALL is described in **Attachment 1**.

The treatment involves cancer fighting medicine called chemotherapy. The treatment on this part of the study takes about 2 years and is divided into the following 7 phases. The details of Consolidation, Interim Maintenance, Delayed Intensification, and Maintenance are described in **Attachment 1**.

The part of this study that is different from standard therapy is the elimination of the second part of Delayed Intensification therapy, and treatment with blinatumomab.

Summary of Study Treatments

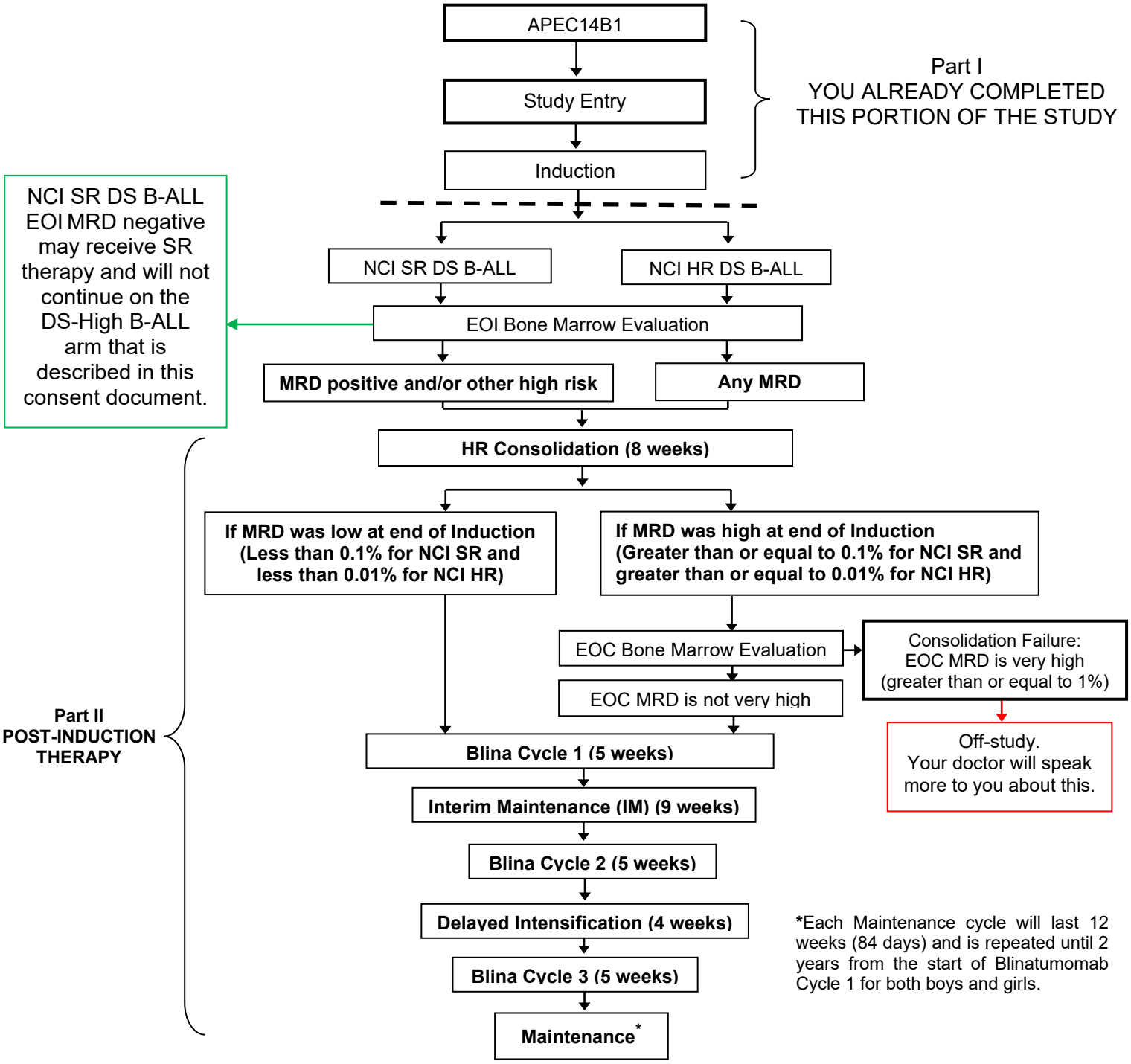
In this study you will get a modified standard chemotherapy with 3 cycles of blinatumomab. The treatment on this study is divided into the following 7 phases, which are described in **Attachment 1**.

- Consolidation
- Blinatumomab Cycle 1
- Interim Maintenance (IM)
- Blinatumomab Cycle 2
- Delayed Intensification (on this study you will only receive Days 1-29)
- Blinatumomab Cycle 3
- Maintenance

Refer to the next page for the diagram of treatment.

Diagram of Treatment

This chart shows the treatment on this study.



Blina: Blinatumomab **HR**: High Risk **SR**: Standard Risk **DS**: Down syndrome
EOC: End of Consolidation **EOI**: End of Induction **IM**: Interim Maintenance
MRD: Minimal Residual Disease

Treatment that is Research

Some of the treatment on this study is different from standard therapy. This part is experimental and may or may not provide benefit to your treatment. The experimental part of the study includes the elimination of the second part of Delayed Intensification therapy, and treatment with 3 cycles of blinatumomab, one after each of Consolidation, IM, and DI phases of therapy.

The following information describes the shortened DI phase and a single cycle of blinatumomab therapy (you will receive a total of three cycles of blinatumomab on this study).

Methods for Giving Medicines:

Various methods will be used to give medicines:

- **PO** - Drug is given by tablet or liquid swallowed through the mouth.
- **IV** - Drug is given using a needle or tubing inserted into a vein. Drugs can be given rapidly over a few minutes ("push") or slowly over minutes or hours ("infusion").
- **IM** - Drug is given into a muscle using a needle.
- **Continuous Infusion IV** - Drug is given using a needle or tubing inserted into a vein continuously over several days. The infusion will be changed at regular intervals by a medical professional. For blinatumomab, the 28-day continuous infusion will include regular trips to a health care facility for bag changes every 4-7 days.
- **IT** - Drug used to treat the brain and spinal cord is given using a needle inserted through the back into the fluid surrounding the spinal cord.

Delayed Intensification

Delayed Intensification lasts about 29 days (or about 4 weeks).

Drug	How drug will be given	Days
VinCRIStine	IV infusion using a minibag over several minutes	1, 8, and 15
Dexamethasone	PO twice a day or IV	1-7 and 15-21
DOXOrubicin	IV over 3-15 minutes	1, 8, and 15
Pegaspargase[1] or Calaspargase pegol [1, 2]	IV over 1-2 hours or IM	4
	IV over 1-2 hours	
Methotrexate	IT	1
Leucovorin	PO or IV	24 & 30 hours after each IT methotrexate

[1] If you develop an allergy to pegaspargase or calaspargase pegol, a different form of asparaginase may be substituted for each dose of pegaspargase or calaspargase pegol.

[2] Calaspargase pegol can only be given to patients under the age of 22 years.

Blinatumomab cycle

The three cycles of blinatumomab will be given to you after Consolidation, IM, and Delayed Intensification. Each cycle lasts 5 weeks. The treatment for a single blinatumomab cycle is described below:

Drug	How the drug will be given	Days
Dexamethasone (Cycle 1 only)	PO (may be given IV)	1
Blinatumomab[1]	IV, 28-day continuous infusion	1-28
Methotrexate	IT	1
Leucovorin	PO or IV	2 (24 & 30 hours after each IT methotrexate)

- [1] Down Syndrome patients ≥ 10 years of age when receiving blinatumomab therapy are required to receive an anti-seizure medication during blinatumomab infusion. The risks and benefits of the different choices of Blinatumomab bags will be discussed with you by your treating team.

You may be hospitalized for at least the first 2 days of Cycle 1 and for at least the first day of Cycle 2 as a precaution. If your level of MRD by flow cytometry testing was greater than or equal to 0.01% before receiving blinatumomab, then you may be hospitalized for at least the first 3 days of Cycle 1 and for at least the first 2 days of Cycle 2 as a precaution. The remainder of standard chemotherapy is described in Attachment 1.

Blinatumomab is a medicine that is given into the body using a needle or tubing inserted into a vein, in bags. Different sized bags can be used. These bags are given over different amounts of time before needing to be changed. The options that can be used on this trial are listed in the table below.

Days	Infusion hours	FDA approved	Contains a preservative called benzyl alcohol
1	24	Yes	No
2	48	Yes	No
3	72	No	No
4	96	No	No
7	168	Yes	Yes

Below are some key things to know about treatment with blinatumomab:

- Total length of a blinatumomab cycle is 28 days.
- In the United States, the Food and Drug Administration (FDA) has approved blinatumomab to be used in bags that give blinatumomab into the body over 24 hours (1 day) and 48 hours (2 days).
- The FDA has also approved blinatumomab to be used in bags that can be given over 168 hours (7 days). These bags contain a preservative called benzyl alcohol that prevents bacteria from growing in the bag.
- In the United States, the FDA has not approved blinatumomab to be used in bags that give blinatumomab into the body over 72 hours (3 days) or 96 hours (4 days). There is a possible risk of bloodstream infections because these bags do not contain the preservative benzyl alcohol.
- The 72 hours (3 days) and 96 hours (4 days) bags have already been used in clinical trials in the United States in hundreds of adults and children without FDA approval.

You should discuss the risks and benefits of the different choices of blinatumomab bags with your treating team to decide what is right for you.

Required Research Study Tests and Procedures

The following required test will be done because you are part of this study. If you were not in this study, you might not have this testing done.

End of Consolidation bone marrow MRD by Flow Cytometry - only for patients with high end of Induction MRD (greater than or equal to 0.1% for NCI SR patients and greater than or equal to 0.01% for NCI HR patients)

We would like to test your bone marrow at the end of Consolidation to see if there are still small amounts of leukemia cells remaining in your bone marrow. We will take 5 mL (about 1 teaspoon) of bone marrow during one of your regular visits. This involves putting a needle into the marrow space of your hip (pelvis) bone and removing (drawing) bone marrow with a syringe. There may be extra pain related with getting the bone marrow, and sometimes a second needle stick may be needed. Samples for this test will be sent to a particular COG-approved lab for testing. We will label them with your name and the results will be provided to your treating physician to share with you. There will be no extra cost to you or your health insurance provider for this study.

If your level of MRD at the end of Consolidation is very high (greater than or equal to 1%), also called Consolidation Failure, you will be removed from study and offered alternative therapy.

Optional Research Study Tests

We would also like to do some tests called quality of life studies. These tests are important to help us learn more about DS-High B-ALL, and may help children and young adults in the future. The information learned will not change the way you are treated, and the results of these tests will not be given to you. You do not have to do these tests if you do not want to. You can still be in the study if you do not want to do these tests. At the end of this consent form, there is a place to record your decision about taking part in each test. There will be no extra cost to you or your health insurance provider for this study.

Longitudinal Neurocognitive Function and Quality of Life in Children with Down syndrome and B-ALL. This study is for patients with DS B-ALL only.

Researchers have studied the effects of ALL therapy on neurocognitive function and quality of life in children with B-ALL, but we would like to know more about the effects in patients with DS B-ALL, who have not been included in past studies. If you agree to participate in this study, you will be asked to fill out questionnaires about your child's thinking, learning, and quality of life. Questionnaires will be completed during regularly scheduled clinic visits. The estimated time to complete these questionnaires is about 60 minutes. The results of these questionnaires will not be returned to you. These questionnaires will be completed a total of 3 times at the following times:

- Cycle 1 of Maintenance phase therapy
- Cycle 5 of Maintenance phase therapy
- One year after the end of therapy visit

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. In addition to killing tumor cells, cancer chemotherapy can damage normal tissue and produce side effects.

The risks of the individual drugs given as standard treatment and risks of radiation therapy are listed in **Attachment 2**.

Common side effects of chemotherapy include nausea, vomiting, hair loss, and fatigue (tiredness). Drugs may be given to try to prevent or decrease nausea and vomiting. Hair loss is usually temporary but very rarely it may be permanent. Some chemotherapy may make people permanently unable to have children. On rare occasions, people can get a

second cancer from chemotherapy. This usually happens years after the chemotherapy is finished. Side effects can be increased when chemotherapy drugs are combined.

The most common serious side effect from cancer treatment is lowering of the number of blood cells resulting in anemia, increased chance of infection, and bleeding tendency. Low blood counts are described in the COG Family Handbook for Children with Cancer. Parents will be taught more about caring for their child when his or her blood counts are low.

Risks of Study

In this study, the elimination of the second part of delayed intensification and the addition of 3 cycles of blinatumomab therapy could be less effective than the current standard treatment and may lead to a lower cure rate. There is also a risk that the use of blinatumomab together with standard chemotherapy may cause more complications.

It is possible that the risk of infection could be more common when using blinatumomab bags that last 72 hours or 96 hours. Bacteria and other infections can grow in some medicines. In these rare events, if bacteria got into a blinatumomab bag, the bacteria would have more time to grow in the bags that are used for a longer time. This could increase the risk of infection.

Many studies have shown the risk of infections with blinatumomab is very low and is less than the risk of chemotherapy.

The use of blinatumomab in patients with Down syndrome who are age 10 years or older may be associated with increased risk of seizure. It is required that patients with Down syndrome who are age 10 years or older receive a medication to reduce the risk of seizure during the time that blinatumomab is administered. Your doctor can explain to you how this medicine can reduce your risk of experiencing a seizure while on this study.

You may lose time at school, work or home and spend more time in the hospital or doctor's office than usual. You may be asked sensitive or private questions which you normally do not discuss. You may not be able to take part in future studies.

The chemotherapy used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drugs/study approach. Here are important points 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 interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

You can ask your study doctor questions about side effects at any time. Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.

- The study doctor will provide you with information about other drugs you may need to avoid while receiving the study drugs.

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

The risks associated with blinatumomab are listed in the tables below.

COMMON, SOME MAY BE SERIOUS In 100 people receiving blinatumomab (AMG 103), more than 20 and up to 100 may have:
• **Anemia which may require blood transfusion** • **Nausea** • **Tiredness, fever** • **Infection, especially when white blood cell count is low** • **Bruising, bleeding** • **Headache**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving blinatumomab (AMG 103), from 4 to 20 may have:
• **Blood clot which may cause swelling, pain, shortness of breath** • **Abnormal heartbeat** • **Pain** • **Constipation, diarrhea, vomiting** • **Sores in the mouth which may cause difficulty swallowing** • **Chills** • **Swelling of the body** • **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat** • **Weight gain** • **Weight loss, loss of appetite** • **Difficulty walking, talking, sleeping** • **Change(s) in thinking patterns, or voice** • **Dizziness, confusion** • **Trouble with memory** • **Abnormal body movement** • **Feeling of "pins and needles" in arms and legs** • **Seizure** • **Worry** • **Internal bleeding which may cause black tarry stool, blood in vomit or blood in urine** • **Cough, shortness of breath** • **Nose bleed** • **Increased sweating** • **Itching, rash** • **Flushing** • **High blood pressure which may cause headaches, dizziness, blurred vision** • **Low blood pressure which may cause feeling faint**

RARE, AND SERIOUS In 100 people receiving blinatumomab (AMG 103), 3 or fewer may have:
• **Damage to the bone marrow which may cause infection, bleeding, may require transfusions** • **Air trapped in internal organs that may cause discomfort or pain** • **Bleeding of the mouth** • **Kidney damage which may require dialysis** • **Bleeding in the brain** • **Damage to organs (brain, lungs) which may cause shortness of breath** • **Damage to the brain or nerves** • **Brain damage which may cause headache, seizure, blindness (also known as Reversible Posterior Leukoencephalopathy Syndrome)** • **Mini stroke** • **Restlessness** • **Sensing things that are not there** • **Change in personality** • **State of mind that involves a "loss of contact with reality"** • **Fluid in the organs which may cause low blood pressure, shortness of breath, swelling of ankles**

In addition to the risks described above, there may be unknown risks, or risks that we did not anticipate, associated with being in this study.

Reproductive risks

Women should not become pregnant and men should not father a baby while on this study because the drug(s) in this study can be bad 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. If you are taking blinatumomab, you should use effective contraception during treatment with blinatumomab and for at least 48 hours after the last dose of blinatumomab. 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. Also check with your doctor about how long you should not breastfeed after you stop the study treatment(s).

You will also be provided with a clinical trial wallet card for this study at enrollment. The card contains important clinical trial information that your other healthcare providers need to know. It's a convenient wallet-sized information card for you to cut out and retain at all times.

Are there benefits to taking part in the study?

We hope that this study will help you personally, but we do not know if it will.

Potential benefits to you could include:

- getting rid of your cancer for a long time or for the rest of your life,
- fewer side effects,
- a shorter duration of treatment,

- fewer long term side effects (for example, being less likely to develop problems with the heart, lungs, kidneys; being less likely to have learning problems, or, less risk of getting another cancer later as a result of treatment).

With any cancer treatment, sometimes treatment does not make the cancer go away. Or, sometimes treatment makes the cancer go away for a while but the cancer comes back later.

We expect that the information learned from this study will benefit other patients in the future.

What other options are there?

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

- **Current standard therapy, even if you do not take part in a study. Standard therapy is described on Attachment 1, except for the second part of DI, which is not included on this study.**
- **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 6,720. The number of patients that will be enrolled on the DS-High B-ALL group of this study will be 150.

How long is the study?

People in this clinical trial are expected to receive treatment on this study for about 2 years. After treatment, you will have follow-up examinations and medical tests.

We would like to continue to find out about your health every year for about 10 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
- 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. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. However, we cannot guarantee total privacy. The *Children's Oncology Group* has a privacy permit to help protect your records if there is a court case. However, some of your medical information may be given out if required by law. If this should happen, the *Children's Oncology Group* will do their best to make sure that any information that goes out to others will not identify who you are. Information about this Certificate of Confidentiality is included in **Attachment 3**.

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**
- **The company providing the study drug (Amgen)**
- **The company that performs HTS MRD testing (Adaptive Biotechnologies)**
- **The company that owns the test used for the Neurocognitive study (CogState)**

In addition to storing data in the study database, data from studies that are publicly funded may also be shared broadly for future research with protections for your privacy. The goal of this data sharing is to make more research possible that may improve people's health. Your study records may be stored and shared for future use in public databases. However, your name and other personal information will not be used.

Some types of future research may include looking at your information and information from other patients to see who had side effects across many studies or comparing new study data with older study data. However, right now we don't know what research may be done in the future using your information. This means that:

- You will not be asked if you agree to take part in the specific future research studies using your health information.
- You and your study doctor will not be told when or what type of research will be done.
- You will not get reports or other information about any research that is done using your information.

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 NCI will supply blinatumomab at no charge while you take part in this study. The NCI does not cover the cost of getting the blinatumomab ready and giving it to you, so you or your insurance company may have to pay for this.

Even though it probably won't happen, it is possible that the manufacturer may not continue to provide the blinatumomab to the NCI for some reason. If this does happen, other possible options are:

- You might be able to get the blinatumomab from the manufacturer or your pharmacy but you or your insurance company may have to pay for it.
- If there is no blinatumomab available at all, no one will be able to get more and the study would close.

If a problem with getting blinatumomab occurs, your study doctor will talk to you about these options.

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. The drug company that makes blinatumomab is providing money to the Children's Oncology Group to do the research. There are no plans to pay you for taking part in this study.

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 at 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).

Optional research tests

The choice to let us collect information from questionnaires 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 questionnaire information 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 questionnaire information. Then, any information that we have will be destroyed.

Please read the information below and think about your choices. After making your decisions, check "Yes" or "No", then add your initials and the date after your answer. If you have any questions, please talk to your doctor or nurse, or call our research review board at the IRB's phone number included in this consent.

#1 I agree to participate in the series of questionnaires for the Neurocognitive Outcomes and Quality of Life in children with Down syndrome and B-ALL study.

Yes_____ No_____ N/A _____ _____ / _____
Initials Date

Signature

I have been given a copy of all _____ pages of this form. The form includes three (3) attachments.

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

Treatment and Procedures Common to all Patients with DS-High B-ALL

Methods for Giving Drugs

Various methods will be used to give drugs:

- **PO** - Drug is given by tablet or liquid swallowed through the mouth.
- **IV** - Drug is given using a needle or tubing inserted into a vein. Drugs can be given rapidly over a few minutes ("push") or slowly over minutes or hours ("infusion").
- **SubQ** - Drug is given by inserting a needle just under the skin.
- **IT** - Drug used to treat the brain and spinal cord is given using a needle inserted through the back into the fluid surrounding the spinal cord.
- **IM** - Drug is given into a muscle using a needle.

Central Line

Your doctor may recommend that you get a special kind of IV called a "central line." This is a kind of IV placed into a big vein in your body, usually in the chest, that can stay in for a long time. The risks connected with central lines will be explained to you and all of your questions will be answered. If you are to have a central line inserted, you will be given a separate informed consent document to read and sign for this procedure. A description of the types of central lines is in the COG Family Handbook for Children with Cancer.

Standard Chemotherapy Treatment Tables – Post-Induction

The therapy described below is considered the standard post-Induction treatment for subjects with DS-High B-ALL. Standard post-Induction treatment is divided into the following phases: Consolidation, Interim Maintenance, Delayed Intensification, and Maintenance.

Side effects may be more severe and the risk of death during therapy may be greater for children with DS. To protect your body from the side effects of methotrexate, DS patients will receive a supportive care medicine called leucovorin at 24 and 30 hours after each intrathecal methotrexate during all phases of therapy. Patients with DS are more likely to have side effects from methotrexate than other patients. Leucovorin may help minimize these side effects; however it may also make methotrexate less effective in treating leukemia.

Consolidation

Consolidation therapy starts after Induction and lasts about 56 days (8 weeks).

Drug	How the drug will be given	Days
Cyclophosphamide	IV over 30-60 minutes	1 and 29
Cytarabine	IV over 1-30 minutes or SubQ	1-4, 8-11, 29-32, and 36-39
Mercaptopurine	PO once a day	1-14 and 29-42
VinCRIStine	IV infusion using a minibag over several minutes	15, 22, 43 and 50
Pegaspargase [1]	IV over 1-2 hours or IM	15 and 43
or Calaspargase pegol[1, 2]	IV over 1-2 hours	
Methotrexate	IT	1, 8, 15 [3], and 22 [3]
Leucovorin	PO or IV	24 & 30 hours after each IT methotrexate
Testicular Irradiation[4]		Given daily for 12 days

[1] If you develop an allergy to pegaspargase or calaspargase pegol, a different form of asparaginase may be substituted for each dose of pegaspargase or calaspargase pegol.

[2] Calaspargase pegol can only be substituted for patients less than 22 years of age.

[3] Omitted in patients with leukemia cells in the CNS.
[4] Males with clinically evident or biopsy proven testicular disease at the end of Induction.

Interim Maintenance

Interim Maintenance with Intermediate Dose methotrexate lasts about 63 days (or about 9 weeks). It requires being in the hospital, so you will have four 2-3 day hospital stays.

Drug	How the drug will be given	Days
VinCRIStine	IV infusion using a minibag over several minutes	1, 15, 29, and 43
Intermediate Dose (ID) Methotrexate	IV over 24 hours	1, 15, 29, and 43
Methotrexate	IT	1 and 29
Mercaptopurine	PO once a day	1-56
Leucovorin	PO or IV	30, 36, 42, 48 & 54 hours after each ID methotrexate

Delayed Intensification

Delayed Intensification for non-DS patients on this study lasts about 56 days (or about 8 weeks). On this study, DS-High B-ALL patients will only receive Days 1-29 therapy.

Drug	How drug will be given	Days
VinCRIStine	IV infusion using a minibag over several minutes	1, 8, and 15
Dexamethasone	PO twice a day or IV	1-7 and 15-21
DOXOrubicin	IV over 3-15 minutes	1, 8, and 15
Pegaspargase [1] or Calaspargase pegol [1,2]	IV over 1-2 hours or IM	4
	IV over 1-2 hours	
Methotrexate	IT	1
Leucovorin	PO or IV	24 & 30 hour after each IT methotrexate

[1] If you develop an allergy to pegaspargase or calaspargase pegol, a different form of asparaginase may be substituted for each dose of pegaspargase or calaspargase pegol.
[2] Calaspargase pegol can only be given to patients less than 22 years of age.

Maintenance

Each Maintenance cycle will last 12 weeks (84 days) and is repeated until 2 years from the start of Blinatumomab Cycle 1.

Drug	How drug will be given	Days
VinCRIStine	IV infusion using a minibag over several minutes	Once every 12 weeks
Prednisone or Prednisolone	PO twice a day[1]	5 days every 12 weeks
Methotrexate	PO	Once a week (except week of IT methotrexate)
Mercaptopurine	PO once a day	1-84
Methotrexate	IT	Day 1 of every cycle and Day 29 [2] of cycles 1-3

Leucovorin	PO or IV	24 & 30 hours after each IT methotrexate
Cranial Irradiation [3]		Daily for 10 days

[1] IV methylprednisolone may be substituted for prednisone or prednisolone at 80% of the oral (PO) dose.
[2] Day 29 doses are only for patients who do not receive cranial irradiation.
[3] Patients with leukemia in the central nervous system (CNS3). Given in the first 4 weeks of Maintenance.

Standard Radiation Therapy

Some patients may need to receive radiation therapy to remove leukemia cells from certain parts of the body.

Patients diagnosed with leukemia in the brain or spinal cord at the beginning of therapy will receive cranial radiation therapy during the first 4 weeks of Maintenance phase therapy.

Any male patients with testicular leukemia at diagnosis and at the end of Induction will receive radiation therapy to the testes during Consolidation. Patients who had testicular leukemia at diagnosis but do not have it at the end of Induction, and who also have a negative testicular biopsy at the end of Induction will not receive testicular radiation therapy.

Standard Tests and Procedures

The following tests and procedures are part of regular cancer care and may be done even if you do not join the study.

- 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.
- Tests to monitor your heart and lung function.
- Bone marrow aspiration tests to see if the cancer is responding to treatment. The bone marrow procedure is described in the COG Family Handbook for Children with Cancer.
- Spinal Taps to check for cancer cells in the spinal fluid and to give chemotherapy into the spinal fluid. This is described in the COG Family Handbook for Children with Cancer.

Attachment 2

Risks of Chemotherapy Drugs and Radiation Used to Treat DS-High B-ALL

Possible Side Effects of Asparaginase erwinia chrysanthemi (recombinant) or Asparaginase Erwinia/crisantaspase

COMMON, SOME MAY BE SERIOUS In 100 people receiving Asparaginase erwinia chrysanthemi (recombinant) or Asparaginase erwinia/crisantaspase, more than 20 and up to 100 may have:
• **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat** • **Infection, especially when white blood cell count is low** • **Bleeding** • **Belly pain, nausea, diarrhea, decreased appetite** • **Sores in mouth which may cause difficulty swallowing** • **Pain in muscles** • **Tiredness** • **Headache** • **Fever**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Asparaginase erwinia chrysanthemi (recombinant) or Asparaginase erwinia/crisantaspase, from 4 to 20 may have:
• **Pain including in the bone** • **Abnormal heartbeat which may cause fainting** • **High blood pressure which may cause headaches, dizziness, blurred vision** • **Low blood pressure which may cause feeling faint** • **Blood clot, including in the brain, which may lead to stroke** • **Acute respiratory distress syndrome which may cause damage to the lungs and shortness of breath** • **Fluid around lungs which may cause shortness of breath** • **Cough** • **Kidney damage which may cause swelling, may require dialysis** • **Possible changes in mental status** • **Dehydration** • **Bloating, constipation** • **Feeling of "pins and needles" in arms and legs** • **Muscle cramp, muscle weakness** • **Difficulty walking** • **Restlessness, difficulty sleeping** • **Worry, irritability** • **Dizziness** • **Itching** • **Swelling and redness at the site of the medication injection**

RARE, AND SERIOUS In 100 people receiving Asparaginase erwinia chrysanthemi (recombinant) or Asparaginase erwinia/crisantaspase 3 or fewer may have:
• **Sinusoidal obstructive syndrome (SOS) which may cause damage to the liver, yellowing of the eyes and skin, swelling**

Possible Side Effects of Pegaspargase or Calaspargase pegol

COMMON, SOME MAY BE SERIOUS In 100 people receiving Pegaspargase or Calaspargase pegol, more than 20 and up to 100 may have:
• **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat** • **Nausea, vomiting** • **Chills, fever** • **Tiredness** • **Hives, rash**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Pegaspargase or Calaspargase pegol, from 4 to 20 may have:
• **Abnormal heart beat** • **Blood clot, including in the brain, which may lead to stroke** • **Infection, especially when white blood cell count is low** • **Bruising, bleeding** • **Anemia which may require blood transfusions** • **Liver damage which may cause yellowing of eyes and skin** • **Belly pain, damage to the pancreas** • **Diabetes**

RARE, AND SERIOUS In 100 people receiving Pegaspargase or Calaspargase pegol, 3 or fewer may have:
• **Sinusoidal obstructive syndrome (SOS) which may cause damage to the liver, yellowing of the eyes and skin, swelling**

Possible Side Effects of Cyclophosphamide

COMMON, SOME MAY BE SERIOUS In 100 people receiving Cyclophosphamide, more than 20 and up to 100 may have:
• **Hair loss, skin changes, rash, change in nails** • **Nausea, vomiting, diarrhea, loss of appetite, pain in belly** • **Sores in mouth which may cause difficulty swallowing** • **Infection, especially when white blood cell count is low** • **Absence of menstrual period which may decrease the ability to have children** • **Blood in urine** • **Bruising, bleeding** • **Anemia which may cause tiredness, or may require transfusion**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Cyclophosphamide, from 4 to 20 may have:
• **Damage to the bone marrow (irreversible) which may cause infection, bleeding, may require transfusions** • **Loss or absence of sperm which may lead to an inability to father children** • **Fluid around the heart**

RARE, AND SERIOUS In 100 people receiving Cyclophosphamide, 3 or fewer may have:
• **Stevens-Johnson syndrome which may cause severe skin rash with blisters and peeling which can involve mouth and other parts of the body** • **Damage to the heart or heart failure which may cause shortness of breath, swelling of ankles, cough or tiredness** • **A new cancer (including leukemia) resulting from treatment of a prior cancer** • **Swelling of the body including the brain which may cause dizziness, confusion** • **Damage to the lungs or scarring of the lungs which may cause shortness of breath** • **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat** • **Kidney damage which may cause swelling, may require dialysis** • **Sinusoidal obstructive syndrome (SOS) which may cause damage to the liver, yellowing of eyes and skin, swelling**

Possible Side Effects of Cytarabine by vein or under the skin

COMMON, SOME MAY BE SERIOUS In 100 people receiving Cytarabine, more than 20 and up to 100 may have:
• **Infection, especially when white blood cell count is low** • **Anemia which may cause tiredness, or may require blood transfusions** • **Bruising, bleeding** • **Blood clot** • **Rash** • **Diarrhea, loss of appetite, nausea, vomiting, pain in belly** • **Sores in mouth, throat, and GI tract including rectum which may cause difficulty swallowing or pain** • **Fever**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Cytarabine, from 4 to 20 may have:
• **Heart failure which may cause shortness of breath, swelling of ankles, cough or tiredness** • **Abnormal heartbeat which may cause fainting** • **Damage to the lungs which may cause shortness of breath** • **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat** • **Numbness and tingling of the arms and legs** • **Muscle pain** • **Severe blood infection** • **Kidney damage which may cause swelling, may require dialysis** • **Headache** • **Dizziness, confusion** • **Flu-like syndrome with fever, bone pain, rash, redness of eyes, or chest pain** • **Chest pain** • **Hair loss** • **Liver damage which may cause yellowing of skin or eyes** • **Swelling and redness of the eye** • **Hives** • **Itching** • **Infection at injection site which may cause rash** • **Difficulty emptying the bladder or urinating**

RARE, AND SERIOUS In 100 people receiving Cytarabine, 3 or fewer may have:
• **Brain damage, Posterior Reversible Encephalopathy syndrome, which may cause headache, seizure, blindness** • **Difficulty speaking, trouble standing or walking, coma** • **Swelling and redness at the site of the medication injection (SubQ)**

Possible Side Effects of Dexamethasone

COMMON, SOME MAY BE SERIOUS In 100 people receiving dexamethasone, more than 20 and up to 100 may have:
• **High blood pressure which may cause headaches, dizziness** • **Skin changes, rash, acne** • **Swelling of the body, tiredness, bruising** • **In children and adolescents: decreased height** • **Pain in belly, heartburn** • **Infection** • **Damage to the bone which may cause joint pain, loss of motion, or broken bones** • **Difficulty sleeping** • **Restlessness, worry** • **Mood swings** • **Diabetes** • **Increased appetite and weight gain in belly, face, back and shoulders** • **Loss of bone tissue**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving dexamethasone, from 4 to 20 may have:
• **Blood clot which may cause swelling, pain, shortness of breath** • **Glaucoma** • **Cloudiness of the eye, visual disturbances, blurred vision** • **A tear or a hole in the bowels which may cause pain or that may require surgery** • **Numbness, pain and tingling of the arms, legs, fingers and/or toes** • **Muscle weakness** • **Non-healing wound**

RARE, AND SERIOUS In 100 people receiving dexamethasone, 3 or fewer may have:
• **None**

Possible Side Effects of Doxorubicin

COMMON, SOME MAY BE SERIOUS In 100 people receiving Doxorubicin, more than 20 and up to 100 may have:
• **Hair loss** • **Nausea, vomiting** • **Red colored urine, saliva, or sweat**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Doxorubicin, from 4 to 20 may have:
• **Heart failure or heart attack which may cause shortness of breath, swelling of ankles, cough or tiredness which may occur years after the dose** • **Abnormal heartbeat** • **Damage to the lungs which may cause shortness of breath when combined with radiation** • **Infection, especially when white blood cell count is low** • **Bruising, bleeding** • **Anemia which may cause tiredness, or may require transfusion** • **Kidney damage which may require dialysis** • **Swelling and redness at the site of the medication injection or area of previous radiation** • **Belly pain** • **Sores in the mouth or throat** • **Diarrhea, dehydration** • **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat** • **Damage to the skin which may cause pain** • **Darkening of the nail beds or skin or hands and feet** • **Changes to the nails** • **Absence of menstrual period or early menopause** • **Damage to sperm** • **Muscle weakness** • **Darkening of the gums**

RARE, AND SERIOUS In 100 people receiving Doxorubicin, 3 or fewer may have:
• **Severe blood infection** • **Damage to the bone marrow, caused by chemotherapy, which may result in leukemia (cancer of the bone marrow)**

Possible Side Effects of Leucovorin

COMMON, SOME MAY BE SERIOUS In 100 people receiving Leucovorin, more than 20 and up to 100 may have:
• **Diarrhea, nausea, vomiting, loss of appetite** • **Sores in mouth which may cause difficulty swallowing** • **Tiredness** • **Blisters on the skin**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Leucovorin, from 4 to 20 may have:
• **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat**

RARE, AND SERIOUS In 100 people receiving Leucovorin, 3 or fewer may have:
• **None**

Possible Side Effects of Mercaptopurine

COMMON, SOME MAY BE SERIOUS In 100 people receiving Mercaptopurine, more than 20 and up to 100 may have:
• **Anemia which may cause tiredness, or may require transfusion** • **Bruising, bleeding** • **Infection, especially when white blood cell count is low** • **Rash** • **Loss of appetite, nausea, vomiting, diarrhea** • **Fatigue**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Mercaptopurine, from 4 to 20 may have:
• **Damage to the liver which may cause pain, bleeding, confusion, yellowing of eyes and skin** • **Increased risk of sunburn** • **Fever**

RARE, AND SERIOUS In 100 people receiving Mercaptopurine, 3 or fewer may have:
• **Scarring of the lungs which may cause shortness of breath** • **Damage to the pancreas causing belly pain** • **A new cancer resulting from treatment** • **Loss or absence of sperm**

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** • **Bleeding into the space of the spine at the site of the injection**

Possible Side Effects of Methotrexate when given by mouth or by vein

COMMON, SOME MAY BE SERIOUS In 100 people receiving methotrexate, more than 20 and up to 100 may have:
• **Loss of appetite** • **Increased risk of sunburn, rash** • **Hair loss**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving methotrexate, from 4 to 20 may have:
• **Heart failure, which may cause shortness of breath, swelling of ankles, cough, or tiredness** • **Fluid around heart** • **Damage to the brain, which may cause tiredness, confusion, changes in mood, anxiety, dizziness, lightheadedness, ringing in the ears, difficulty speaking or understanding speech** • **Weakness on one or both sides of the body** • **Internal bleeding which may cause belly pain, black tarry stool, blood in vomit** • **Sores in mouth which may cause difficulty swallowing** • **Hepatitis or damage to the liver which may cause yellowing of eyes and skin, swelling** • **Scarring of the lungs or damage to the lungs, which may cause shortness of breath, cough** • **Low blood oxygen, which may cause shortness of breath, headache, confusion, or restlessness** • **Blood in urine** • **Bruising, bleeding** • **Infection, including pneumonia, especially when white blood cell count is low** • **Anemia which may cause tiredness, or may require transfusion** • **Seizure** • **Kidney damage which may require dialysis** • **Blood clot, possibly in the brain or lung, which may cause swelling, pain, shortness of breath** • **Low blood pressure, which may cause feeling faint** • **Blurred vision or other visual changes, possibly including temporary blindness** • **Swelling and redness of the whites of the eye** • **Nausea, vomiting, diarrhea, weight loss, heartburn, belly pain** • **Menstrual changes** • **Flu-like symptoms, including fever, chills, body aches, muscle pain, tiredness** • **Headache** • **Numbness and tingling of the skin**

RARE, AND SERIOUS In 100 people receiving methotrexate, 3 or fewer may have:
• **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat** • **Stevens Johnson syndrome which may cause severe skin rash with blisters and peeling which can involve mouth and other parts of the body**

Possible Side Effects of Methylprednisolone

COMMON, SOME MAY BE SERIOUS In 100 people receiving methylprednisolone, more than 20 and up to 100 may have:
• **In children and adolescents: decreased height** • **Loss of bone tissue which may lead to increased bone fractures** • **Joint pain** • **Mood swings, depression, worry** • **Skin changes, acne, rash** • **Swelling of the body from fluid retention, tiredness, bruising** • **High blood pressure which may cause headaches, dizziness, blurred vision** • **Pain in belly, bloating, nausea, hiccups** • **Increased appetite and weight gain in the belly, face, back and shoulders** • **Difficulty sleeping, restlessness** • **Dizziness** • **Increased sweating** • **Changes in hair growth, hair loss**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving methylprednisolone, from 4 to 20 may have:
• **Blood clot which may cause swelling, pain, shortness of breath** • **Fluid around lungs which may cause shortness of breath** • **Cloudiness of the eye, visual disturbances, blurred vision** • **Glaucoma** • **Infection** • **A tear or a hole in the bowels which may cause belly pain or that may require surgery** • **Non-healing wound** • **Diabetes** • **Numbness and tingling of the arms, legs, and upper body** • **Muscle weakness** • **Heartburn**

RARE, AND SERIOUS In 100 people receiving methylprednisolone, 3 or fewer may have:
• **Bleeding from sores in the stomach**

Possible Side Effects of Prednisone or Prednisolone

COMMON, SOME MAY BE SERIOUS In 100 people receiving prednisone or prednisolone, more than 20 and up to 100 may have:
• **In children and adolescents: decreased height** • **Loss of bone tissue** • **Mood swings** • **Skin changes, acne** • **Swelling of the body, tiredness, bruising** • **High blood pressure which may cause headaches, dizziness, blurred vision** • **Pain in belly** • **Increased appetite and weight gain in the belly, face, back and shoulders** • **Difficulty sleeping**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving prednisone or prednisolone, from 4 to 20 may have:
• **Irregular heartbeat** • **Heart failure** • **Blood clot which may cause swelling, pain, shortness of breath** • **Cloudiness of the eye, visual disturbances, blurred vision** • **Glaucoma** • **Infection** • **Non-healing wound** • **Diabetes** • **A tear or a hole in the bowels which may cause belly pain or that may require surgery** • **Damage to the bone which may cause joint pain and loss of motion** • **Numbness and tingling of the arms, legs and upper body** • **Muscle weakness** • **Heartburn**

RARE, AND SERIOUS In 100 people receiving prednisone or prednisolone, 3 or fewer may have:
• **Tiredness and low blood pressure which may cause feeling faint** • **Bleeding from sores in the stomach** • **Broken bones**

Possible Side Effects of VinCRIStine

COMMON, SOME MAY BE SERIOUS In 100 people receiving VinCRIStine, more than 20 and up to 100 may have:
• **Constipation, which may be severe, as a result of a bowel blockage** • **Nausea, vomiting, diarrhea** • **Hair loss** • **Pain or redness at the site of injection** • **Numbness and tingling of fingers or toes** • **Headache, jaw pain and/or bone/muscle pain** • **Muscle weakness and difficulty walking** • **Swelling of lower legs**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving VinCRIStine, from 4 to 20 may have:
• **High blood pressure which may cause headaches, dizziness, blurred vision** • **Low blood pressure which may cause feeling faint** • **Anemia which may cause tiredness, or may require blood transfusions** • **Swelling that may be accompanied by confusion, and dizziness** • **Paralysis** • **Loss of appetite, weight loss** • **Difficulty with emptying the bladder or urinating, excessive, frequent, or painful urination** • **Drooping eyelids, abnormal eye movement** • **Hoarseness** • **Difficulty with balance and hearing**

RARE, AND SERIOUS In 100 people receiving VinCRIStine, 3 or fewer may have:
• **Seizure** • **Coma** • **Visual loss with a chance of blindness** • **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat**

Possible Side Effects of Radiation Therapy (RT)

COMMON, SOME MAY BE SERIOUS In 100 people receiving radiation therapy, more than 20 and up to 100 may have:
• **Reddening, tanning, or peeling of the skin** • **Mild pain** • **Hair loss** • **Tiredness** • **Diarrhea, nausea** • **Anemia, which may require transfusion** • **Infection, especially when white blood cell count is low** • **Difficulty having children or inability to have children**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving radiation therapy, from 4 to 20 may have:
• **Thickening and numbness of the skin** • **Sores or ulcers on the skin or near the cancer location** • **Permanent hair loss** • **Bleeding from the skin** • **Sores in mouth which may cause difficulty swallowing**

RARE, AND SERIOUS In 100 people receiving radiation therapy, 3 or fewer may have:
• **Damage to internal organs** • **Abnormal opening in internal organs which may cause pain and bleeding**

CNS Radiation

Radiation therapy may produce the following side effects: nausea, vomiting, diarrhea, generalized redness or dryness of the skin, bone marrow failure (absent blood counts resulting in increased risk of infection, weakness and bleeding), loss of hair (which may take 6 months or more for full re-growth), parotitis (swelling of salivary glands) causing jaw pain and swelling, damage to major body organs which may include the brain, eyes, heart, lung, liver and kidneys, and reddening of the skin. There is also the risk of temporary worsening of neurological symptoms such as weakness or loss of sensation. Some children experience a week or two of low grade temperature and extreme sleepiness 6 to 8 weeks after radiation therapy has been completed.

Possible late effects may include: shortened height (growth retardation), back bone change of shape (vertebral deformities), difficulty with vision (cataracts), changes in endocrine function (low hormones), inability to have children (sterility), learning disabilities or brain damage, and increased risk of developing another cancer.

Testicular Radiation

Radiation to the testes is likely to affect both fertility and hormone production. Most boys who have this form of treatment are not able to father children later on since sterility has been associated with testicular radiation. Some may need to take hormones.

Attachment 3

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.