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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: B-ALL 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	19 20	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-ALL and the treatment of patients with localized B-cell Lymphoblastic Lymphoma (B-LLy)

Part I: Consent for Induction for Subjects with B-Lymphoblastic Leukemia with or without Down syndrome (DS)

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 one of the following:

- **Standard Risk B-cell Lymphoblastic Leukemia (SR B-ALL)**
- **B-cell Lymphoblastic Leukemia and you have Down syndrome (DS B-ALL) of any risk level**

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 Part I of this study is to collect information about your leukemia and your response to the first phase of treatment, called Induction.

Part I of the study is necessary to determine if you will be eligible for in Part II, and to help decide the best treatment after Induction.

The treatment involves cancer fighting medicines called chemotherapy. The treatment on this part of the study takes about one month.

All people who receive cancer treatment are at risk of having side effects. Cancer chemotherapy kills tumor cells. In addition to killing tumor cells, cancer chemotherapy also can damage normal parts of the body and cause side effects.

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

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**.

We hope that this study will help you personally, but we do not know if it will. The potential benefits to you that may happen if you participate in this study are described in the section Are there benefits to taking part in the study?

You have a choice between a standard treatment for 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.

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 either Standard Risk B-cell Lymphoblastic Leukemia (SR B-ALL) or B-cell Lymphoblastic Leukemia and you have Down syndrome (DS B-ALL) of any risk level.

B-ALL is a cancer of the white blood cells. White bloods cells help fight infections. White blood cells are made in the bone marrow. The bone marrow is the soft tissue in the center of the bones. With B-ALL, white blood cells can change. Instead of being normal, they become abnormal. These abnormal white blood cells are called blasts. The blasts grow and divide. The blasts crowd out normal bone marrow cells. The blasts spread into the blood stream. Blasts can also spread to the brain, spinal cord, testes, and other places in the body. For this study, you either have leukemia that is classified as Standard Risk (SR) because your white blood cell count is less than 50,000/microliters and you are between 1 and 10 years old, or you have Down syndrome and have leukemia of any risk level. The term risk refers to the chance of the cancer coming back after treatment.

This study is called a clinical trial. A clinical trial is a research study involving treatment of a disease in people. 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 teenagers with cancer in a clinical trial that seeks to improve cancer treatment over time. Clinical trials include only people who choose to participate. You have a choice between a standard treatment for your 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. The first phase of treatment for B-ALL is called Induction and lasts 5 weeks. The goal of Induction is to remove all visible signs of leukemia. This allows normal blood cells to be restored. This is called *remission*. Five chemotherapy drugs are used during Induction. **The chemotherapy given during Induction is the same for patients who do not choose to be on this study.**

The rest of therapy is called post-Induction (Part II). The goal of post-Induction therapy is to get rid of any remaining leukemia cells and keep the leukemia from coming back. Post-Induction therapy has several phases that are called Consolidation, Interim Maintenance (IM I & II), Delayed Intensification (DI), and Maintenance. All phases of treatment are very important.

Why is this study being done?

This study is being done in multiple parts. This consent is for Part I. Part I is the Induction phase of therapy.

The purpose of Part I of this study is to collect information on the leukemia and how it responds to the treatment. To enroll on this study, you need to first sign a consent form for the study APEC14B1 (Project:EveryChild). This other study will be explained to you in a different consent.

We will collect blood tests and bone marrow tests to see how fast the leukemia is responding to the treatment. This is done by a test called minimal residual disease (MRD). The MRD results will also be used to determine the risk group of your leukemia at the end of Induction. Your doctor will explain the results of the test. Your doctor will explain what your risk group means. The MRD test will also help doctors understand why some chemotherapy drugs are not as good for some patients. MRD testing is explained in detail in the “Research Study Tests and Procedures” section.

The overall goal of Part I of this study is to collect information about your leukemia and your response to the first phase of treatment, called Induction.

You may be offered the chance to take part in Part II of this study after Induction once your B-ALL risk group is known. Depending on your risk group there is a chance that you may be randomized to receive the investigational medicine, blinatumomab plus standard treatment

during Part II. Randomization means you will have an equal chance of receiving or not receiving blinatumomab.

In Part II of this study, all patients will be treated with the same length of therapy for boys and girls. The standard duration of treatment in COG ALL trials has been gender-based, with girls receiving 2 years and boys receiving 3 years of treatment after the start of Interim Maintenance I. However, recent analyses of past studies have shown that the additional year of therapy for boys may not lead to improvements in their outcome with our modern therapies. In addition, other groups in other parts of the country and the world currently do not give additional therapy to boys. We hope that eliminating the additional year of therapy for boys on this study will result in fewer long term side effects. We will be monitoring boys closely on this study to see if they have higher rates of the leukemia returning compared to boys previously treated with three years of therapy.

Your medical team will discuss this with you, and you will receive another consent form with more information about post-Induction therapy in Part II. You will have a chance to decide if you want to continue with the study at that time.

What will happen on this study that is research?

The treatment involves cancer fighting medicine called chemotherapy. The treatment for Part I of the study takes about 5 weeks (4 weeks of therapy).

Subjects (people participating in the study) will receive standard treatment for SR B-ALL or DS B-ALL during Induction. Treatment that is standard is described in **Attachment 1**.

The major goal of Induction therapy is to use a combination of chemotherapy drugs to try to eliminate as many of the leukemia cells as possible. We will also collect information from you that may be used to help further define your risk group. Your risk group helps decide the best treatment after Induction.

Some testing of your leukemia cells will be done as part of APEC14B1 (Project:EveryChild), which will require additional blood and bone marrow to be taken at diagnosis when blood and bone marrow are already being collected for clinical care.

Required Research Study Tests and Procedures

The following tests are required. They are needed to determine your risk group. Assigning a risk group assignment will be done because you are part of this study. If you were not in this study, you might not have MRD testing done to determine your risk group and the treatment you receive after Induction. Most doctors treating patients with your type of leukemia send MRD testing for patients not on clinical trials as well.

Minimal Residual Disease (MRD) using Flow Cytometry

This test measures very small amounts of leukemia cells found in your bone marrow and/or blood. MRD tells us how quickly the leukemia is responding to therapy. From past COG studies, we have learned that subjects with higher levels of MRD do worse than subjects with lower levels of MRD. Sometimes, MRD is used to change therapy. Sometimes different drugs or

more drugs are given to patients with higher levels of MRD. This will be explained to you after we have the results of the MRD tests.

Testing the bone marrow on Day 29 for MRD by flow cytometry is considered standard. This means most doctors would do the test if you were on this study or not. You or your health insurance provider will be responsible for the cost of this test. Day 29 bone marrow samples will be sent to a COG-approved laboratory for this MRD testing. In addition to the Day 29 bone marrow testing, we will also test your blood on Day 8 for MRD if you are either SR B-ALL or DS B-ALL that is standard risk (if you have DS B-ALL that is high risk, we will not perform the Day 8 MRD test). We will label them with your name and the results will be provided to your treating physician to share with you. These MRD test results will be used to help determine which risk group you belong to after you have completed Induction therapy.

Bone Marrow MRD using High Throughput Sequencing (HTS)
On this study, doctors will collect additional bone marrow at the same time the sample is being collected for Day 29 of Induction therapy to test MRD using flow cytometry. They will use these samples to look at changes in MRD using a different test called HTS. HTS can detect even smaller numbers of leukemia cells than the standard flow cytometry test. The results of the HTS MRD will be sent to your doctor to share with you. It will take 2-4 weeks for this test. The results will be returned to you by the end of the next phase of therapy. The next phase of therapy is called Consolidation therapy. HTS MRD testing is more sensitive than the standard flow cytometry method. We think this may help study doctors to better define your risk of relapse (cancer coming back). The HTS will be used in some patients to be offered the chance to receive treatment with the study drug blinatumomab in a later phase of the study. There will be no extra cost to you or your health insurance provider for this test.

Optional Research Study Tests
We would also like to do some tests called biology studies and quality of life studies. These tests are important to help us learn more about B-ALL. These may help children and young adults in the future. The information learned will not change the way you are treated. 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 the optional studies.

Household Material Hardship and Neurocognitive Outcomes– non-DS patients ages 4 to less than 10 years old who are receiving treatment in the U.S. or Canada and speak English, Spanish, or French are eligible
Nearly 1 in 3 families experience problems with money or financial stress during their child's cancer treatment. This may include lost income from work, difficulty paying the rent or mortgage, difficulty keeping the electricity or heat on or putting food on the table. Financial stresses or problems with money can affect both adults and children in many ways. Study doctors are hoping to learn about how these stresses change during the years of ALL treatment. We know that leukemia therapy can affect children's attention, memory and how they learn in the future (neurocognitive function). Stress can also affect memory and attention. We would like to understand how leukemia therapy and financial stresses might interact to affect different parts of memory and attention. We hope that in the future, this information will help doctors to better prevent learning difficulties after treatment or to reduce them as much as possible. We also hope this information will help study doctors find ways to decrease the financial impact of treatment on each family, and to make sure that financial stress does not impact a child's experience during treatment.

If you decide to participate in this study, you will be asked to complete a household questionnaire 4 times during your regular clinic visits (about every 6 months). The questionnaire includes questions about your family supports, housing, home utilities (electricity/heat), food, finances, stress, and coping. We will also ask you to fill out a questionnaire about your child's everyday thinking and learning. The questionnaires will take about 20-35 minutes to complete. Children will be asked to complete short tests of attention and memory on the computer that last about 25-30 minutes. Right before they take the computer test, we will ask your child questions about any physical symptoms they are feeling, like pain or nausea. Children will not be asked to do these computer tests until they reach 4 years of age. The results of these questionnaires and computer tests will not be returned to you. All of your survey answers will be confidential, and your answers will not be shared with your treatment team. Survey data will not be placed in your medical record. Before we analyze the survey data for research, they will be de-identified, which means that no information that would permit identification of your family or child will be shared. You will be asked to complete questionnaires and your child will be asked to complete the computer test once during the Induction phase of therapy and 3 times during later phases of treatment.

If you choose to participate in this study, you may also be offered a chance to participate in the Caregiver Burden and Symptom Assessment portion of this research study after Induction, depending on the risk group you are assigned after Induction.

Down Syndrome Immune Function Study – **DS patients only**
Children with DS are at a higher risk of developing infections while receiving chemotherapy treatment than children without DS. With your permission, we would like to take an additional blood sample of 10 mL (about 2 teaspoons) to look at how your immune system works and to try to find out why DS children develop more infections. The immune system is the part of the body that fights infections. This blood will be collected during your regular visits at the same time as standard blood tests are done to avoid the risks of an extra needle stick. The blood will be collected at two time points, listed below:

- Before the start of Induction therapy at diagnosis
- On Day 1 of the second cycle of Maintenance therapy

The results of this test will not be returned to you because we do not yet know if this result should affect your treatment.

Biobanking for Future Research
We would like to take some of your tissue for future research. This is called "specimen banking" or "tissue banking." A tissue bank is a lab where specimens (such as tumor, blood or bone marrow) are kept for use in future research studies.

Biobanking for future research on end of Induction blood – **non-DS patients only**
With your permission, we would like to collect an extra 3-5 mLs (½-1 teaspoon) blood sample on Day 29 of treatment for specimen banking. This blood will be collected during your regular visit at the same time as standard blood tests are done to avoid the risks of an extra needle stick.

Biobanking for future research on CSF**– non-DS patients only**
Cerebrospinal fluid (CSF) is the fluid that surrounds the brain and spinal cord. As part of your treatment, chemotherapy will be given intrathecally (into the spinal cavity) using a procedure called a lumbar puncture (sometimes called a spinal tap) where a needle is inserted through the

back and into the spinal cavity. As part of your regular tests, CSF will be collected during a lumbar puncture at the same time as scheduled chemotherapy treatment. With your permission, we will not remove any extra CSF, but we are asking your permission to bank any leftover CSF (usually 2.5 mL, or about ½ teaspoon) that is not used for routine laboratory studies. These will be collected once during the Induction phase of therapy and 3 times during later phases of treatment.

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 cause side effects.

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

Though combining chemotherapy drugs is the most effective way to kill leukemia cells, side effects can also be increased when chemotherapy drugs are combined.

The most common serious side effect from cancer treatment is lowering of the number of normal blood cells resulting in anemia, increased chance of infection, and bleeding. 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 Associated with the Research Study

The risks associated with the drugs used in this study to treat B-ALL are the same as those associated with standard therapy for B-ALL. These include an increased risk of infection, low levels of healthy blood cells, and possible damage to bones or joints. The chemotherapy used in this study may also 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.

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.

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 tables in Attachment 2 show 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.

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. 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. 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 treatments.

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 in Attachment 1.**
- **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 about 6,720.

How long is the study?

Induction therapy will last about 4 weeks. After Induction, your doctor will know your B-ALL risk group, and you may be given the chance to continue on subsequent parts of this clinical trial. You will need to get more therapy for leukemia whether or not you take part in subsequent parts of this trial. 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
- 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. 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 that owns the test used for the Neurocognitive study (CogState)**
- **The company that performs HTS MRD testing (Adaptive Biotechnologies)**

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.

There will be no additional cost to you for the neurocognitive 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.

This study includes providing specimens to researchers. 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).

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 and banking, 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.

If you want to learn more about tissue research with banked specimens, the NCI website has an information sheet called "Providing Your Tissue For Research: What You Need To Know." This sheet can be found at: https://www.cancer.gov/publications/patient-education/providing-tissue .

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 **Household Material Hardship and Neurocognitive Outcomes study**

For patients without Down syndrome, age 4 to less than 10 years old receiving treatment in the U.S. or Canada who speak English, Spanish, or French: I agree to participate in the Household Material Hardship and Neurocognitive Outcomes study.

Yes_____ No_____ N/A_____ _____ / _____
Initials Date

#2 For patients with Down syndrome: My blood may be collected and used for the Down Syndrome and Immune Function Study.

Yes_____ No_____ _____ / _____
Initials Date

Specimens for optional biobanking

If you agree to Biobanking, your sample will be stored *in the Biopathology Center at Nationwide Children's Hospital, in a locked freezer*. The samples *will be kept until they are used up*, unless you request that they be destroyed. Some information from your medical record, including your name, date of birth, and unique COG identifier, will also be kept in secure databases at the Biobank and updated from time to time. The information and samples will be kept under a code, not your name.

For certain studies, the Children's Oncology Group partners with biopharmaceutical (drug) companies that are developing new anti-cancer drugs. When we partner with drug companies, COG may provide specimens or data to the drug company to help with the research. The data may include information about the type of cancer you have, your treatment and how your cancer responded. The drug company will not be given your name or any other information that could directly identify you.

This is a publicly funded study. Samples from publicly funded studies are required to be shared as broadly as possible. Qualified researchers can submit a request to use the materials stored in the Biobank. The research may be about your type of cancer, about other cancers, or even about conditions unrelated to cancer. The goal of this is to make more research possible that may improve people's health. A science committee at the Children's Oncology Group, and/or the National Cancer Institute, will review each request. Researchers will not be given your name or any other information that could directly identify you. Your sample will not be sold to third parties. Neither you nor your study doctor will be notified when research will be conducted or given reports or other information about any research that is done using your samples, unless something is discovered that could directly affect your health. If that happens your study doctor will be notified and will decide whether and how to contact you.

Right now, we don't know what research may be done in the future using your samples. 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.

Unknown future research studies may include sequencing of all or part of your DNA. This is called genomic sequencing. Sequencing allows researchers to identify your genetic code. Changes in your genetic code may just be in your tumor tissue. These are called somatic changes. Changes may also be in your normal tissue and passed down through your family. For example, these genetic changes may be passed down to your children in the same way that eye and hair color are passed down. These are called germline changes. If only tumor tissue is sequenced, we will not know if a genetic change in your tumor is also in your normal tissue. This is why sometimes both normal tissue and tumor tissue are sequenced. This helps researchers understand if a genetic change happened only in your cancer tissue, or in your normal tissue as well.

Some of your genetic and health information may be placed in central databases that may be made available to qualified researchers, along with information from many other people. Information that could directly identify you will not be included.

Even without your name or other identifiers, your genetic information is unique to you. If you agree to Biobanking, there is a risk of a data security breach and that someone could trace the genetic information in a central database back to you. Although this has never happened in real life and we have many safeguards in place to prevent it from happening, the risk may change in the future as people come up with new ways of tracing information. There are laws against the misuse of genetic information, but they may not give full protection. In some cases, misuse of the information could be used to make it harder for you to get or keep a job or insurance.

There can also be risks in learning about your own genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a study. Sometimes this is upsetting to families or they wish they didn't know the information. We encourage you to discuss this study with your relatives before you decide whether to participate in the Biobanking part.

If you want to learn more about tissue research with banked specimens, the NCI website has an information sheet called "Providing Your Tissue For Research: What You Need To Know." This sheet can be found at: https://www.cancer.gov/publications/patient-education/providing-tissue.

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) For patients without Down syndrome: Check YES if you agree to have additional peripheral blood and leftover CSF samples kept (banked) for use in research to learn about, prevent, or treat cancer or other health problems (for example: diabetes, Alzheimer's disease, or heart disease). Check NO if you do not want any samples banked.

Yes _____ No _____ _____ / _____
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 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").
- **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 Treatment Tables

The treatment described below is standard treatment for patients with newly diagnosed SR B-ALL and DS B-ALL. The purpose of Induction phase therapy is to kill as many of the leukemia cells as possible so the disease goes into remission.

Studies have shown that subjects who have DS are more likely to suffer serious side effects from treatment with chemotherapy than subjects without DS. Subjects with DS are particularly sensitive to certain chemotherapy medications, such as methotrexate. To help lessen the side effects of methotrexate, you will be given a supportive care medicine called leucovorin if you have DS, 24 and 30 hours after you are given methotrexate into your spinal fluid. Although leucovorin may help with side effects, it may also make methotrexate less effective in treating leukemia.

Induction for non-DS SR B-ALL

Induction therapy starts on Day 1 and lasts about 35 days (or about 5 weeks).

Drug	How the drug will be given	Days
Cytarabine	IT	1 and twice weekly [1]
Vincristine	IV infusion using a minibag over several minutes	1, 8, 15, and 22
Pegaspargase [2]	IV over 1-2 hours or IM	4
or Calaspargase pegol [2,3]	IV over 1-2 hours	
Dexamethasone	PO twice a day or IV	1 - 28
Methotrexate	IT	8 and 29

[1] In addition to the initial dose on Day 1, subjects with CNS2 (a moderate level of leukemia in the brain or spinal fluid) receive Cytarabine twice weekly until 3 consecutive CSF samples are clear of blasts.
Note: IT Cytarabine will not be administered on Days 8 and 29 when IT Methotrexate is administered.

[2] 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.
[3] Calaspargase pegol can only be given to patients less than 22 years of age.

Induction for DS B-ALL

Induction therapy starts on Day 1 and lasts about 35 days (or about 5 weeks).

Drug	How the drug will be given	Days
Cytarabine	IT	1 and twice weekly [1]
Vincristine	IV infusion using a minibag over several minutes	1, 8, 15, and 22
Pegaspargase [2]	IV over 1-2 hours or IM	4
or Calaspargase pegol [2,3]	IV over 1-2 hours	
Dexamethasone **For patients <10 years old**	PO twice a day or IV	1-28
Prednisone or Prednisolone **For patients ≥ 10 years old**	PO twice a day or IV [4]	1-28
Methotrexate	IT	8 and 29 [5]
Leucovorin	PO or IV	24 and 30 hours after each IT MTX

[1] In addition to the initial dose on Day 1, subjects with CNS2 receive Cytarabine twice weekly until 3 consecutive CSF samples are clear of blasts. **Note:** IT Cytarabine will not be administered on Days 8 and 29 when IT Methotrexate is administered.
[2] 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.
[3] Calaspargase pegol can only be given to patients less than 22 years of age.
[4] If you cannot take oral prednisolone, IV methylprednisolone may be given instead
[5] CNS3 (a high level of leukemia in the brain or spinal fluid) patients also receive this on Days 15 and 22

You will be examined at the end of Induction therapy to find out your remission status. Remission is when there are no more leukemia cells seen in the bone marrow or spinal fluid.

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.
- Ultrasound of the testes for patients with suspected testicular leukemia
- 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 Used to Treat 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** • **Belly pain, nausea, diarrhea, decreased appetite** • **Infection, especially when white blood cell count is low** • **Bleeding** • **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:
• **Abnormal heartbeat which may cause fainting** • **High blood pressure which may cause headaches, dizziness, blurred vision** • **Low blood pressure which may cause feeling faint** • **Pain including in the bone** • **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 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 Cytarabine when given into the spinal fluid (intrathecal)

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

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Cytarabine, 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, 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 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** • **Mood swings** • **Restlessness, worry** • **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 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 of 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 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 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** • **Increased sweating** • **Changes in hair growth, hair loss** • **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**

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 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**

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.