IWK Health Centre

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Information Sheet and Consent Form

PEDIATRIC IBD REGISTRY

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Co-Investigator: **Mohsin Rashid, MD FRCPC**
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Division of Gastroenterology
Department of Pediatrics
IWK Health Centre

Introduction:

You are being invited to take part in the research study named above. It is important that you understand the purpose of the study, how it may affect you, the risks and benefits of taking part and what you will be asked to do, before you decide if you want to take part. This information and consent form is to help you decide if it is in your best interest to take part in this study. You do not have to take part in this study. Taking part is entirely optional. If you have any questions that this form does not answer, the research staff or study investigator will be happy to give you further information.

The purpose of the study

The object of this study is to follow a large group of pediatric inflammatory bowel disease patients to get a clearer understanding of the disease course in children and adolescents, and the effect both in terms of quality of life and economic burdens of its management.

Study Design

This is an observational research study. This means that disease-related information on the pediatric participants will be tracked over the study period. Your care will not be altered in any way by entering this study. Your physician will manage your care as they would under normal practice conditions. No extra visits, procedures, or treatments are required.

This study is being conducted in 22 sites across North America. Up to 2 500 children and adolescents with inflammatory bowel disease will take part, with 250 participants from the IWK GI Clinic. There is no set end date for this study. New participants will be added and older participants who no longer wish to be involved will leave the study.

You will be followed from the time of diagnosis until the completion of the study or until you choose to withdraw from the study. Participants will be enrolled who agree to be followed for at least two. Those 9 years of age or older must be able and willing to fill out the quality of life questionnaire at the beginning of the study and every six months after that, until their 18th birthday, while they remain in the study (please see next section for more details on this questionnaire).

What Participation Involves

Participation in this study will take two forms:

1. As described above, during the study period disease-related information will be tracked for all participants. The initial registration form and subsequent data are faxed to the study coordination centre. Thereafter, this information will be tracked every three months. Information will be obtained by clinic visits, chart review or by direct communication with you or your parent (by phone or e-mail).
2. Children 9 years of age and older will be asked to complete a quality of life questionnaire every six months until their 18th birthday. The first time this will be done will be either at the beginning of the study for children 9 years of age and older, or following their 9th birthday. After this, every six months you will be sent the questionnaire. It takes between 10 and 15 minutes to complete.

Potential Harms

Because this is an observation study we do not anticipate any harms from participating. We think it is unlikely that you will be distressed by answering the quality of life questionnaire, but if any questions or issues arise you or your parent/guardian can contact a member of the IWK IBD program for assistance (902-[redacted] or [redacted] Monday to Friday 8:00 am to 4:00 pm).

Potential Benefits

There is no guarantee you will experience any benefit from participating in this study. However, the information gained may help physicians understand the disease course in children and adolescents, and the effect both in terms of quality of life and economic burdens of its management.

Alternatives to Participation

Before deciding to enroll in this study, you should know that you do not have to take part in the study. The alternative is simply not to participate.

Withdrawal from Participation

Participation in the study is entirely your choice. You may decide to withdraw from the study at any time without affecting your care by your doctor or at the IWK Health Centre in any way. If the study is changed in any way which could affect your decision to continue to participate, you will be told about the changes and you may be asked to sign a new consent form.

Costs and Reimbursement

Participation in this study will not result in any expenses to you. At the end of each year the participant's study number will be entered into an annual draw. Five participants will each be awarded $10.00.

Confidentiality
Study staff will have access to your study and medical records. In addition, the records may be shown to personnel of the Research Services Office of the IWK Health Centre and health authorities in Canada and the United States, such as Health Canada. By signing this form, you authorize this access.

To register you in the study your initials and birth date will be sent by fax on a study registration form to the Child Health Data Center at the Connecticut Children's Medical Center. This is the organization that has been contracted by the researchers to coordinate the study. The quality of life questionnaire will be sent to you every six months.

If you choose to be contacted by email, your parent/guardian will also be copied on that email. Due to the nature of electronic communication, absolute confidentiality cannot be guaranteed. Providing your email address is entirely your choice.

If the results of the study are published in the medical literature the publication will not contain any information that would identify you. Study records will be stored in a locked area and will be kept for 5 years after the last date that the data is used for the study.

Research Rights
Your signature on this form will show that you have understood to your satisfaction the information about the research study. Agreeing to participate in this study does not mean that you waive your legal rights nor does it release the investigator, or other involved parties from their legal and professional responsibilities.

If you have any questions at any time during or after the study about research in general and you would like an independent opinion, you may contact the Research Office of the IWK Health Centre at 470-8765, Monday to Friday between 9 am to 5 pm.

Contact Person
If you have any questions or concerns following your enrollment, you may contact the GI Research Assistant at [redacted] or Dr. Otley at the IWK Health Centre at [redacted], Monday to Friday between 9:00 am to 5:00 pm.

Participant Consent

I have read or had read to me the information and consent forms and have had the chance to ask questions which have been answered to my satisfaction before signing my name. I understand the nature of the study. I understand that I have the right to withdraw from the study at any time without affecting my care in any way. I have received a copy of the information and consent forms for future reference. I freely agree to participate in this research study.

Name of Participant (Print): [redacted]

Participant Signature: [redacted]

Date: [redacted] Time: [redacted]

I may be contacted via the following e-mail address:

Participant: [redacted]

STATEMENT BY PERSON PROVIDING INFORMATION ON STUDY

I have explained the nature and demands of the research study to the participant named above and answered all of their questions.

Name (Print): [redacted]

Signature: [redacted] Position: [redacted]

Date: [redacted] Time: [redacted]

STATEMENT BY PERSON OBTAINING CONSENT

I have explained the nature of the consent process to the participant and judge that they understand that participation is voluntary and that they may withdraw at any time from participating.

Name (Print): [redacted]

Signature: [redacted] Position: [redacted]

Date: [redacted] Time: [redacted]

INFORMATION AND CONSENT FORM

Study Title: A Randomized, Multicentre, Open-Label Study to Evaluate the Safety and Efficacy of Anti-TNFα Chimeric Monoclonal Antibody (Infliximab, Remicade®) in Pediatric Subjects with Moderate to Severe Crohn's Disease

Investigators: Anthony Otley MD, MSc, FRCPC
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Division of Gastroenterology, Department of Pediatrics
IWK Health Centre and Dalhousie University

Sponsor: Centocor, Inc

Introduction

You are being asked to take part in the research study named above. It is important that you understand the purpose of the study, how it may affect you, the risks and benefits of taking part and what you may be asked to do, before you decide if you want to take part. This information and consent form is to help you decide if it is in your best interest to take part in this study. Taking part is entirely voluntary (your choice). If you have any questions that this form does not answer, the research nurse or study investigator will be happy to give you further information.

Purpose of the Study

The purpose of this study is to evaluate the safety and effectiveness of an antibody called infliximab (Remicade®) in the treatment of children with Crohn's disease. The safe use of infliximab is well-established in adults with moderate to severe Crohn's disease as well as in the treatment of rheumatoid arthritis. Infliximab is given to children with Crohn's disease although the safety and effectiveness have not been proven in children. Infliximab has not been approved by Health Canada for use in children.

Crohn's disease is characterized by inflammation and ulceration in the digestive tract. It is treated with medications that decrease the inflammation such as sulfasalazine. Other medications such as steroids (prednisone) or immunomodulators (azathioprine) decrease the inflammation by suppressing the immune system.

A naturally occurring substance in our immune system called tumor necrosis factor-alpha (TNFα) is thought to be involved in chronic inflammation and is believed to be one of the causes of the symptoms of Crohn's disease. Infliximab has been developed to control inflammation by decreasing the effect of TNFα. Infliximab is an "antibody". An antibody is a substance produced by the immune system. Infliximab is a chimeric antibody, which means the antibody is made in part from mouse protein and in part from human protein.

Study Design

One hundred and ten (110) children between the ages of 6-17 years of age with moderate to severe Crohn's disease will be invited to take part in this study. The study will be conducted across North America, Western Europe and Israel. Participants will receive 3 doses of infliximab followed by regular infusions at either 8-week or 12-week intervals. Giving a medication by infusion means giving it through a vein in the hand or the arm. The primary goal of the study is to ensure infliximab is safe and effective in children when given over an extended period of time. Other goals studied will be 1) to evaluate the effectiveness of giving the infusions at 8 or 12 week intervals 2) to see whether steroid use can be decreased 3) to track side effects and your growth over one year. Knowing the answer to these questions will determine if infliximab is a safe and effective treatment for children with moderate to severe Crohn's disease.

There is an Open-Label Extension of this study. Open-Label means that you will be receiving infliximab and not a placebo, the same as in the main part of the study. If you are eligible to participate in the Open-Label Extension, infliximab may be given for up to three additional years or until the drug is approved for use in children in Canada (whichever comes first). To be eligible, you must have completed all assigned infusions in the main study AND the study doctor must agree that this will be the best treatment for you. The Open-Label Extension would extend the time of your participation in this study to a maximum of 4 years. During this time, you may not participate in any other research studies that involve taking medications. See the attached Addendum to this Information and Consent Form for procedures if you participate in the Open-Label Extension.

What Participation Involves

You will be asked to participate in this study for a maximum of 62 weeks in the main study. You will receive an initial 3 doses of infliximab, then you will be placed randomly (like a flip of a coin) in one of two groups and receive infliximab at either 8 or 12 week intervals. The infusions will be given in the clinic and your parent or guardian will be required to accompany you to these visits.

Before the start of the study, you will be required to attend a screening visit to ensure that you meet the rules for entering the study. During this visit, you will have a complete physical examination, a full medical history will be taken and blood and stool samples will be sent to the laboratory. If you are a female of childbearing age, a blood pregnancy test will be done. If the pregnancy test is positive, participation in the study cannot proceed. Appropriate pregnancy counseling will be provided. This screening visit is expected to take about 2 hours.

Unless you have had a chest x-ray taken within three months of the first study infusion and a skin test for tuberculosis (TB) called a PPD (purified protein derivative) in the past month, these tests will need to be done before the start of the study. The PPD test is done by injecting a small amount of tuberculin bacillus under the skin of the forearm. **This test must be read within 48-72 hours after receiving the PPD either by study staff or your family doctor.** If you have been previously exposed to TB, have had a previous infection due to TB, or have received a BCG vaccination in the past, there may be a reddened area around the site of the injection. If the TB skin test and/or the chest x-ray suggest either exposure to, or infection with TB, you will not be eligible to participate in this study. We will arrange for further evaluation and possible medical treatment.

On the first treatment visit (week 0), the rules for entering the study will be reviewed to make sure that you are still eligible for the study. If so, a wrist x-ray will be done to determine bone age and you will then receive the initial dose of infliximab. The infliximab is given through a small flexible tube into a vein (IV) inserted by the study doctor or nurse. The infusion takes a minimum of 2 hours and you must remain in the infusion area for one hour after the infusion. You will be closely monitored during and after the infusion.

The first infusion will take place within 2 weeks after the screening visit. Infusions will be given at week 0 (first treatment visit), week 2 and week 6. If your symptoms have improved when you are seen at the 10 week visit, you will be placed randomly (like a flip of a coin) in one of 2 groups. Group 1 will receive infusions every 8 weeks, that is weeks 14, 22, 30, 38 and 46. Group 2 will receive infusions every 12 weeks, that is weeks 18, 30, and 42. No group will receive infusions after week 46. The infusion visits will take about 4 hours and the non-infusion visits, about 2 hours.

An additional visit (week 62) will be necessary approximately 16-20 weeks after the last dose of study drug for an additional blood test. You will receive a phone call after the week 62 visit to check on any side effects that might have occurred from having blood drawn.

Approximately 13 tablespoons (190 cc) of blood will be taken during the study. Blood samples will be taken to monitor your health, check the drug level in the body and understand the way infliximab decreases the inflammation in the body. Samples of your blood and serum (the clear portion of the blood) will be stored at the study sponsor (Centocor). Your stored samples will only be tested to better understand whether the study drug may cause unexpected safety concerns or how infliximab works; such as by testing for certain substances that may be present or absent in the blood of people with Crohn's disease. No genetic tests will be done on your samples. Your blood and serum will be stored at the sponsor's facility indefinitely (as long as the sponsor decides to store it). If the sponsor decides that it no longer wishes to store your blood and serum, your samples will be destroyed according to standard medical practices. If you decide at any time that you would like your samples to be destroyed, please contact the study doctor.

You will also be asked to fill out a questionnaire called IMPACT. This consists of 35 questions about how you are feeling and how your disease is affecting your life. The questionnaire will take about 10-15 minutes to complete.

If you participate in the Open-Label Extension, there will be 14-20 visits, depending on the dosing schedule. You will be on the same schedule (every 8 or 12 weeks) as during the main study unless you lose response between infusions. In that case, you may be given a larger dose of infliximab or receive infusions more often. . If you participate in the Open-Label Extension phase of the study, the duration of the study will be a maximum of 206 to 210 weeks.

The following is the schedule of appointments and treatments required for this study:

For those in Group 1:

ASSESSMENTS	Screen	WEEK 0	2	6	10	14	22	30	38	46	54	62
Informed consent	X											
Stool culture	X											
TB skin test	X											
Serum pregnancy test	X											
Randomization					X							
Infusions		**X**	**X**	**X**		**X**	**X**	**X**	**X**	**X**		
Medical history	X											
Physical exam	X	X	X	X	X	X	X	X	X	X	X	
Patient assessment		X	X	X	X	X	X	X	X	X	X	
Parent assessment		X	X	X	X	X	X	X	X	X	X	
Doctor assessment		X	X	X	X	X	X	X	X	X	X	
IMPACT scale		X			X			X			X	
Medication diary review		X	X	X	X	X	X	X	X	X	X	
Laboratory tests												
Blood tests	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test		X	X	X		X	X	X	X	X	X	
Urine tests		X	X		X							
X-Rays												
Chest	X*											
Wrist	X*										X	

- If not done within 3 months of enrollment

If you participate in the Open-Label Extension, the infusions will remain on the same schedule, that is, every 8 weeks.

For those in Group 2:

ASSESSMENTS	Screen	WEEK								
		0	2	6	10	18	30	42	54	62
Informed consent	X									
Stool culture	X									
TB skin test	X									
Pregnancy test(blood)	X									
Randomization					X					
Infusions		**X**	**X**	**X**		**X**	**X**	**X**		
Medical history	X									
Physical exam	X	X	X	X	X	X	X	X	X	
Patient assessment		X	X	X	X	X	X	X	X	
Parent assessment		X	X	X	X	X	X	X	X	
Doctor assessment		X	X	X	X	X	X	X	X	
IMPACT scale		X			X		X		X	
Medication diary review		X	X	X	X	X	X	X	X	
Laboratory tests										
Blood tests	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test		X	X	X		X	X	X	X	
Urine tests		X	X		X					
X-Rays										
Chest	X*									
Wrist	X*								X	

- If not done within 3 months of enrollment in study.

If you participate in the Open-Label Extension, the infusions will remain on the same schedule, that is, every 12 weeks.

Those who do not respond to infliximab or lose response according to the protocol (study design):

If your symptoms do not improve, according to he study guidelines, after the first 10 weeks, you will be discontinued from the study and no further infusions will be given. You will be asked to return to the clinic 8 weeks after your last infusion (week 14) for a safety evaluation which will include a physical examination, blood tests for routine safety evaluations and a review of any side effects that might have occurred.

If after week 10, you respond well to the first three infusions by having a decrease in symptoms but those symptoms then return at or before 8 weeks from the last infusion, you will receive the higher dose every 8 weeks until week 46. If you have a return of symptoms between 8 and 12 weeks after the last infusion, you will receive the same dose of medication every 8 weeks instead of every 12 weeks.

You cannot receive the study infusion within 4 weeks of a previous infusion. You will be able to change to a higher dose or a more frequent dosing schedule only one time in the main study.

It **may** be necessary for you to come for an additional visit so that your study doctor or designee can perform a physical examination and arrange laboratory testes to assess your condition. This would be performed in order to determine whether you are eligible to receive a higher dose of infliximab or receive it more frequently.

You must keep a medication diary that will log any changes in your medication, especially doses of steroids. **You must bring this diary with you at every visit for the study doctor/ nurse to review.** In addition, if you change the dose of any of your medications or need to start any new medications (including other investigational drugs) you must ask the study doctor before this happens. **If you see a doctor during the study other than your study doctor, you must tell the doctor that you are taking part in a research study and inform the study doctor promptly.**

Potential Harm:

Any experimental treatment has potential risks. Every effort will be made to make the risks as small as possible. You will be informed of any new findings that may affect your decision to continue in this study.

You may have mild pain, bleeding, bruising, and or an infection at the place where the needle enters the vein. This may happen when the study infusion is given, or when blood is taken. The infusion of infliximab may cause discomfort, bruising, "pins and needles" sensation, numbness or mild infection around the place where the needle enters the vein. Ametop® can be applied with a sticky patch to the area one hour before the blood is drawn and before the infusion to reduce the discomfort.

If you are now taking medicine for your Crohn's disease, stopping the medicines may make your Crohn's disease worse.

Like all medicines, infliximab can have side effects. Most side effects are mild to moderate. Some may be serious and may require treatment or additional testing. Side effects may appear up to six months or longer after the last infusion.

Infections/Tuberculosis

Because infliximab decreases the body's immune response, there is increased risk of infection to those who receive this treatment. The increased risk of infection lasts approximately 8 weeks after infusions. You should also be aware that infliximab can act to lower the body temperature. Therefore, one of the usual signs of infection (fever) may not be present.

Common infections seen with this treatment are colds, sinus infections, sore throat and pneumonia. If you have a fever, feel very tired or unwell, have a cough, have flu-like symptoms, or dental problems you may be getting an infection. You should tell your study doctor right away.

Some patients have had serious infections while receiving infliximab. Some of the patients have died from these infections.

Tuberculosis (TB) is a serious infection. TB is a disease due to an infection that usually involves the lung but can occur elsewhere in the body and may require hospitalization and long-term antibiotic therapy. You may be more prone to tuberculosis while on infliximab. If you or any of your family have ever had tuberculosis you should tell your doctor. While in this study, if you come in contact with anyone who has tuberculosis, you should tell your study doctor. If you have a persistent cough, weight loss, tiredness, fever, chest pain, night sweats, or symptoms of any other infection tell your study doctor and family physician right away. You will be asked questions at every study visit (every 8 weeks or every 12 weeks) regarding possible TB symptoms and whether or not you have been exposed to TB.

Your doctor will examine you and perform a skin test to see if you have ever been exposed to tuberculosis. If you have a positive skin test, you may experience mild pain, itching, redness and slight swelling at the site of the skin test. The skin test is applied under the skin with a small needle. You may have mild pain, bleeding, a change in skin color or bruising, and/or an infection from this test. If your skin test is positive you will not be able to take part in this study. Your doctor will also ask you questions related to tuberculosis. A chest x-ray will be taken to see if there is tuberculosis in your lungs.

There are fungal infections that you may be more likely to develop. The risk is unknown. Two types of these infections are called histoplasmosis and coccidioidomycosis. You should tell your doctor if you live in or have visited or lived in an area where these infections are common. If you don't know if the area you live in is one where these fungal infections are common, ask your doctor. Tell your study doctor immediately if you develop a cough, fever, chills, night sweats, weight loss, chest pain, shortness of breath, or fatigue.

You should also tell your doctor if you have ever had chickenpox. If while in the study you come in contact with someone with chickenpox tell your study doctor.

Tell your doctor or dentist that you are in this study, before you have any surgery or dental procedures.

Congestive Heart Failure

Patients with congestive heart failure (CHF), a disease where the heart pumping action is weakened, were treated with infliximab in another study. Some of these patients had worsening of their CHF and some died. The risk is unknown. If you have a history of CHF or have received treatment for CHF, you are not allowed to participate in this study.

New cases of heart failure have been reported in patients receiving infliximab. It is not known whether or not these cases are related to infliximab. If you have shortness of breath or swelling in your ankles and/or feet, you must contact your study doctor right away.

Allergic Reactions

Some patients have reactions during or 1-2 hours after a treatment. These reactions may include headache, nausea, flushing, light-headedness, shakiness, irregular heartbeats, chest tightness and shortness of breath. These reactions are usually mild or moderate. They occur more often after the first infusion. They can be controlled by slowing the infusion or by giving medication.

Some patients may have severe allergic reactions. This type of reaction may include hives, rash, wheezing, difficulty breathing, swallowing or lower blood pressure.

Some people have had severe allergic reactions, which can be life-threatening. Rare cases of seizures have also been reported. The study doctor will be prepared to treat you promptly if a reaction occurs. If a life-threatening reaction occurs, the infusion will be stopped and the study discontinued. You will be required to return for follow-up blood work. The study nurse will monitor you closely during the infusion. These reactions are usually short-lived.

If you have an allergic reaction your doctor may give you an antihistamine (medication used to treat allergic symptoms such as hay fever). Acetaminophen or paracetamol (medications used to reduce aches, pains, and fever) may also be given. Antihistamines can make you sleepy, so please use caution when driving a car or operating machinery.

Some people develop a delayed hypersensitivity reaction, which is a reaction occurring 1 to 14 days after the infusion. This reaction might include symptoms such as fever, rash, headache, sore throat, muscle or joint pain, hand and face swelling or difficulty swallowing. If any of these signs develop, you must contact the study doctor and your family doctor immediately.

Side effects may appear up to six months or longer after the last infusion. Previous studies in adults have shown that infliximab may cause side effects such as headaches, temporary rash, nausea, flushing, light-headedness and shakiness. Chest tightness and breathlessness, particularly during infliximab infusions (allergic reactions) have also occurred. These reactions are treated with anti-histamines (drugs that decrease the symptoms of allergic reactions) and/or with acetaminophen (Tylenol®) and/or by slowing down the infusion. If you have a reaction, the doctor may give these medications before the next infliximab infusion to help prevent a second allergic reaction from occurring.

While the safety and effectiveness of dosing with infliximab every 8 weeks has been established in adults, it is unclear if people (adults and children) who receive infliximab every 12 weeks will respond the same way. Previous studies in children have shown that long intervals between treatments with infliximab (greater than 5 months and in some cases 1 to 2 years between infusions) resulted in a high rate of infusion reactions and delayed hypersensitivity reactions. Safety data in adults treated with infliximab infusions of up to 16 weeks have not shown this high rate of infusion reactions or delayed hypersensitivity reactions.

Lupus-Like Reactions/Abnormal Blood Test Results

Some patients treated with infliximab have developed a response in which their body "attacked" itself (autoimmunity), which resulted in lupus-like symptoms. Lupus is an inflammatory disease that may be associated with symptoms such as fever, weakness, joint pains or arthritis and rashes. The symptoms generally went away after infliximab treatment was stopped.

Central Nervous System

Some patients, who have a disease of their nervous system, have reported that this disease got worse. You should tell your doctor if you have a disease of your nervous system. Seizures and multiple sclerosis are examples of nervous system diseases.

Rarely, people who did not have a nervous system disease developed one after taking infliximab. Signs of nervous system disease include changes in your vision, weakness in your arms and/or legs, and numbness or tingling in any part of your body. Contact your study doctor right away if you have any of these symptoms.

Vaccinations

Due to risk of infection, you must not receive vaccination with any live viral or bacterial vaccine during the study or for 3 months before the study or for 3 months after your last study infusion. Examples of live viral or bacterial vaccines include: measles-mumps-rubella (MMR), oral polio vaccine (OPV), BCG, typhoid, yellow fever, small pox and chicken pox. You may also be at risk of infection if anyone in your household receives a live virus vaccine. The oral polio vaccine should not be given to anyone living in your household due to the risk of infection to you. In this circumstance, the other polio vaccine, eIPV, is an alternative. Similarly, the chicken pox vaccine should not be given to anyone living in your home due to the rare risk of transmitting the infection to you. If vaccinations with any of the live viral or bacterial vaccines are recommended for you or household contact during the course of the study, you should discuss the risks and alternatives with your personal and research physician. Other types of vaccines are allowed. While you are taking part in the study, contact your study doctor before receiving any vaccines. If you receive a live vaccine you will not receive further study medication.

Antibodies against Infliximab

Infliximab is made partly of mouse protein and partly of human protein. It is possible that your own immune system will develop antibodies (proteins involved in the body's defense mechanism) against infliximab. These antibodies might cause an allergic reaction if you receive mouse proteins in the future (including infliximab). Some people who have received infliximab for their Crohn's disease have developed antibodies to infliximab; your family physician should always be told that you have been treated with mouse antibodies.

Cancer

Lymphoma (a blood cancer) has occurred rarely in patients treated with infliximab. Although rare, it occurred more often than expected for the general population. The patients who developed lymphoma in clinical trials had rheumatoid arthritis, Crohn's disease or psoriatic

arthritis. It is known that patients with rheumatoid arthritis, Crohn's disease, or psoriatic arthritis develop lymphoma more often than expected for the average person.

A very aggressive type of lymphoma, called hepatosplenic T-cell lymphoma, has occurred rarely in adolescent and young adult patients with Crohn's disease who have been treated with infliximab and azathioprine or 6-mercaptopurine. Almost all of these patients have died because of this cancer. It is unclear what role infliximab may have had in the development of the lymphoma or in the deaths. Centocor has not received reports of this type of cancer in patients treated with infliximab with other diseases.

Other types of cancers have occurred infrequently in patients treated with infliximab. In one clinical trial studying infliximab in patients with a specific type of lung disease called COPD (Chronic Obstructive Pulmonary Disease), more patients developed cancer in the group who received infliximab (5%) than the group who received placebo (1%). All patients in the study had a high risk of developing cancer because they were either current or past heavy cigarette smokers.

It is not known whether infliximab played a part in the development of lymphoma or other cancers. If you take part in a clinical study with infliximab, your risk for developing lymphoma or other cancers may increase. If you have COPD, discuss with your doctor if taking part in this clinical study is right for you.

You should tell your doctor if you have a history of lymphoma or cancer prior to participating in this study and if you develop lymphoma or cancer during or after you have participated in this study.

Liver

If you currently or any time in the past have had any liver problems, including hepatitis B, you should tell your doctor.

Some patients develop abnormal liver blood tests, often without symptoms. If this happens, your doctor may stop your treatments for a period of time or permanently. In most cases the liver tests return to normal after stopping treatment.

There have been rare cases where people taking infliximab have developed serious liver problems, some fatal. Signs that you could be having a problem include jaundice (skin and eyes turning yellow), dark brown urine, right-sided stomach pain, fever, and extreme tiredness. If you develop any of these signs, let your doctor know right away.

Blood Problems

In some patients the body may fail to produce enough of the blood cells that help your body fight infection or help you stop bleeding. Some of the patients have died from this failure to produce blood cells. If you develop a fever that doesn't go away, bruise or bleed very easily or look very pale, let your doctor know right away.

IMPACT III Questionnaire

It is unlikely that you will feel distressed by filling out the IMPACT questionnaire, but if any questions or issues arise, you can talk them over with the study doctor or nurse.

Other Risks

There may be other discomforts or risks to you from this study that we do not yet know about. Your study doctor and staff will ask you about any side effects you have at every visit. If you have any problems, you should let the doctor know right away.

Pregnancy and Nursing

If you are pregnant or nursing, you cannot take part in this study. You should not become pregnant during this study or for 6 months after your last study treatment.

The effects of infliximab on fetuses or nursing infants are unknown.

You should not nurse a baby while in this study. You should not become pregnant while in this study. You must discuss methods of contraception with the study doctor and use contraception if you are a woman of child-bearing age. If you think you may have become pregnant while in this study, tell your study doctor right away. The study nurse will discuss birth control with you before and during the study, as appropriate

If you suspect that you are pregnant, notify the study physician or nurse immediately. If any pregnancy test done during the study is positive, the infliximab infusion cannot be given and the study will be discontinued. Appropriate counseling will be offered. If you have begun menstruation or begin menstruating during the trial, a urine pregnancy test will be done before each infusion. You should notify the study doctor or nurse if you begin menstruating during the trial.

Male contraception:

You should not father a child while in this study or for 6 months after your last study treatment.

The effects of infliximab on human sperm are unknown. Men must discuss contraception methods with the study doctor and use contraception while on this study. If you think you may have fathered a child while in this study, tell your study doctor right away.

Potential Benefits

Individuals taking part in this study may or may not receive benefit. A possible benefit is improvement in your Crohn's disease. Studies in adults with Crohn's disease have shown a rapid and long-lasting decrease in symptoms after receiving infliximab. As well, those adults who have had fistulas as a complication of Crohn's disease have shown a reduction in the number of fistulas. The knowledge gained from your taking part may help other patients with Crohn's disease in the future.

Alternatives to Participation:

You do not need to take part in this study. You will receive the same level of care whether or not you choose to take part. Your doctor will discuss with you possible medical, nutritional or surgical options that may exist as appropriate to treat your disease.

These alternate options include other medications which affect the body's immune system, such as azathioprine or methotrexate. You are already on one of these agents, as they are a requirement of entry into the study.

Possible nutritional treatments could include enteral (tube) feedings. Tube feedings involve giving a specially formulated liquid by way of a tube into the stomach. It is possible the formula will cause diarrhea and not be tolerated.

Surgical treatments could include resection (removal of part of the intestine). A potential side effect is infection. Surgery is usually a last resort in Crohn's disease because of the significant risk of recurrence of disease and therefore the need for further surgery.

You are free to withdraw from the study at any time. Infliximab is available outside of this study.

Withdrawal from Study

You may withdraw from the study at any time. As well, the study will be discontinued for the following reasons:

1) Severe infusion reaction
2) Delayed hypersensitivity reaction
3) Centocor decides to discontinue the study
4) The study doctor feels it is your best interest
5) A diagnosis of active TB is made
6) You are exposed to active TB
7) Malignancy (cancer)
8) Pregnancy
9) Crohn's disease related surgery except for abscess drainage and seton placement
10) Development of signs of congestive heart failure
11) Need to take prohibited medication i.e., immunomodulators other than Imuran, 6-MP, methotrexate or any investigational drug
12) Development of any disease or condition in which the investigator feels that your health or well-being may be threatened by continuation of study infusions.
13) More than 12 weeks (not including the 1 week allowable visit window) separating study infusions or more than 1 missed infusion

If you decide to stop getting the study infusions or your study doctor decides to stop giving the infusions, you will be discontinued from the study. If this happens, you must come to the study clinic for an early discontinuation visit. You must also return to the clinic 8 weeks after the last infusion for a safety evaluation and 16 weeks after the last infusion for blood tests. You will receive a phone call after the final visit to check on any side effects that might have occurred from having blood drawn. After you discontinue, you may receive a phone call from the study site to follow up on certain side effects that may have occurred during the study.

If you withdraw permission for any reason after starting in the study, we will not collect any further information about you. However, study information that has been collected and entered in the study cannot be withdrawn.

There is no expiration to your consent. You may cancel permission at any time by contacting the study doctor at the address below or by contacting the GI Research Nurse at 902-[redacted] or the Research Assistant at [redacted]

Dr. Anthony Otley
GI Division, Main Floor
IWK Health Centre
PO Box 9700

Halifax, NS B3K 6R8
Phone [redacted]

If you withdraw from the study for any reason that will not affect in any way the care you receive by the IWK doctors.

Confidentiality:

The information obtained from this study will be made available to Centocor (the study sponsor) and to local and possibly foreign government health agencies that approve the use of new drugs. Your data may also be transferred to other members of the Johnson and Johnson group of companies or to contractors working on their behalf. Any information that leaves the Health Centre will not have your name on it, but will instead be identified by a unique study number. The study information about you will also be available to the researchers and to the IWK Research Ethics Board if they require the information for an audit. Centocor may inspect your study records for the purpose of monitoring the study and analyzing the results. Your study records could also be examined by regulatory authorities to check that the study is being carried out correctly. Except for the above situations, your name and all other personal data will be kept confidential and will not be made publicly available, unless disclosure of this information is required by law. If the results of this study are used for publication, for example in medical journals, your identity will remain confidential. Despite efforts to keep your personal information confidential, absolute confidentiality cannot be guaranteed.

You have the right to request access to your personal information through the study doctor and to correct any inaccuracies that might exist.

Study reports will be stored in a locked area and will be kept for 10 years after the age of majority (19) or for a minimum of 25 years (whichever is longer) as required by Health Canada. By signing this informed consent you authorize this access. The study physician will inform your family doctor of your participation in this study.

Costs and Reimbursement:

The study drug and all examinations, procedures and tests done solely for the purposes of this study will be provided at no cost to you. However, any costs for regular treatment of your Crohn's disease will be your responsibility or the responsibility of your health insurance company. At the end of the study neither Centocor, the sponsor of this study, nor its affiliates is responsible for supplying infliximab for further treatment.

Given the severe nature of your disease, frequent clinic visits would be part of the usual care you would receive. Since three of the study visits are considered "extra", that is, not part of usual care, you will be compensated $30.00 per visit ($90.00 total), payable at the end of the study. If you discontinue your participation in the study for any reason, you will be paid $30.00 for the "extra" study visits you attended.

Communication of Results:

The results of this study will be presented at an Annual IBD Information Night session. These evenings are held every year to allow the team to provide information of clinical and research interest to patients and their families.

Continued Access

The study medication, infliximab, will be provided without charge for the duration of the main study and the Open-Label Extension. Once you have completed the study, infliximab is a licensed product for adults and is available for children in Canada.

Conflicts of Interest:

The researchers do not have any financial interest in the sponsor, Centocor; however, the study doctor is being compensated for conducting this study. Funds received from this study will be used by the study physician to do further research into Inflammatory Bowel Disease.

Research Rights:

Your signature on this form will show that you have understood to your satisfaction the information about the research study. Every effort will be taken by the study doctor, study personnel, and Centocor, Inc. (the study sponsor) so that you are not hurt during this study. Reimbursement for medical expenses associated with the treatment of adverse reactions to the study drug during the study will be provided by the sponsor, Centocor, if in the opinion of the investigator and the sponsor, the reaction was caused by the proper use of the drug in accordance with the terms of the study. If an adverse reaction occurs which was not related to the study drug, or was a result of the study protocol not being properly followed, reimbursement for medical expenses will not be the responsibility of Centocor; in this case, the costs would be borne by yourself, your private health insurance or the provincial health coverage, as appropriate. Financial compensation for such things as lost wages, disability or discomfort due to the injury is not routinely available.

By signing this document, you are not waiving any of your legal rights, nor are you releasing the investigator, institution or sponsor from their legal and professional responsibilities.

If you have any questions at any time during or after the study about these legal rights or about research in general, you may contact the Research office at the IWK Health Centre at 902-[redacted] Monday to Friday between 9 am and 5 pm.

Contact Person:

If you have any questions or concerns following your enrolment in this study, between 9 am and 5 pm Monday to Friday you may call the GI Research Nurse, [redacted] at [redacted] or the GI Research Assistant at [redacted] In an emergency, you may contact the gastroenterologist on call at the Health Centre by calling [redacted] and asking for him to be paged.

Study Title: A randomized, Multicentre, Open-Label Study to Evaluate the Safety and Efficacy of Anti-TNFα Chimeric Monoclonal Antibody (Infliximab, Remicade®) in pediatric Subjects with Moderate to Severe Crohn's Disease

SUBJECT ID: _ [redacted] **SUBJECT INITIALS** [redacted]

Participant Consent

I have read or had read to me this information and consent form and have had a chance to ask questions which have been answered to my satisfaction before signing my name. I understand the nature of the study and I understand the potential risks or reactions. I understand that I have the right to withdraw from the study at any time without affecting my care in any way. I have received a copy of this information and consent form for future reference. I freely agree to participate in this research study.

___ [redacted] _____ [redacted] _____

Name of Participant (Print) Signature of Participant

Date: [redacted] Time: _ [redacted] _____

STATEMENT BY PERSON PROVIDING INFORMATION ON STUDY

I have explained the nature and demands of the research study and judge that the Participant named above understands the nature and demands of the study.

Name (Print) _ [redacted] _ Position _ [redacted] ___

Signature: _____ [redacted] Date: _ [redacted] _ Time: [redacted]

STATEMENT BY PERSON OBTAINING CONSENT

I have explained the nature of the consent process to the participant and judge that they understand that participation is voluntary and that they may withdraw at any time from participating.

Name (Print) __ [redacted] _ Position __ [redacted] __

Signature: _ [redacted] _____Date: _ [redacted] _____

INFORMATION AND CONSENT FORM

TITLE OF STUDY: A Multi-Center, Double-Blind Study to Evaluate the Safety, Efficacy and Pharmacokinetics of the Human Anti-TNF Monoclonal Antibody Adalimumab in Pediatric Subjects with Moderate to Severe Crohn's Disease. Protocol M06-806 Amendment 4

SHORT TITLE: Adalimumab for Treatment of Active Crohn's Disease in Children and Teenagers

SPONSOR: Abbott Laboratories
100 Abbott Park Rd., Abbott Park, IL 60064

INVESTIGATOR: Anthony Otley, MD, MSc, FRCPC
Division of Gastroenterology, Department of Pediatrics
Dalhousie University and IWK Health Centre

CO-INVESTIGATOR: Mohsin Rashid MD, MEd, FRCPC
Division of Gastroenterology, Department of Pediatrics
Dalhousie University and IWK Health Centre

INTRODUCTION

You are being invited to take part in the research study named above. This form provides you with information about the study. Before you decide if you want to take part, it is important that you understand the purpose of the study, the risks and benefits of taking part and what may be asked to do. You do not have to take part. Taking part is entirely voluntary (your choice) and the choice of your parents. You may decide not to take part or you may withdraw from the study at any time. This will not affect the care you will receive from the IWK Health Centre in any way. Informed consent starts with the first contact about the study and continues until the end of the study. A staff member of the research team will be available to answer any questions you or your parents have. You may take home an unsigned copy of this form to think about or discuss it with your family before making a decision.

WHY ARE THE RESEARCHERS DOING THE STUDY?

You have Crohn's disease and are currently being treated. Despite this treatment, you are still having signs and symptoms of Crohn's disease (for example: stomach pain, diarrhea, and tiredness). It is believed that adalimumab may help patients with Crohn's disease who have not had complete relief of their symptoms with the medications that are currently available.

You have been invited to take part in a research study of an experimental (investigational) drug called adalimumab [ad-a-**lim**-u-mab] to treat Crohn's disease. Adalimumab was approved for use in adults with Crohn's disease in Canada on July 5, 2007. It has not yet been approved for use in children in Canada. The study doctor is being paid by Abbott Laboratories to participate in this study. If you decide that you want to take part in this study, you will be asked to sign this consent form to confirm that you have been informed about this study and have given your permission to take part. Your parent(s) will also be asked to sign an authorization form to confirm that they are willing to have you take part in this study. A copy of the signed consent form will be given to you.

A substance called "tumor necrosis factor" (TNF) naturally occurs in the body and is thought to be involved in chronic inflammation. Crohn's disease is chronic inflammation involving the gastrointestinal tract. Antibodies are normally made in the body and help fight infection. Adalimumab is an antibody that is made in a laboratory. It attaches to TNF, making it difficult for TNF to do any damage. The purpose of this study is to evaluate the safety and effectiveness of adalimumab for the treatment of moderate to severe Crohn's disease in children and adolescents aged 6 to 17 years, inclusive. In addition, information will be collected to select the most effective dose of adalimumab. If it is found that adalimumab is effective in treating moderate to severe Crohn's disease, this will provide a new treatment option for the disease. You must be between 6-17 years of age at the time of the first dose of medication.

HOW WILL RESEARCHERS DO THE STUDY?

This study is sponsored by Abbott Laboratories and is being conducted at about 55 treatment centers in the United States, Canada and Europe. Approximately 184 children and adolescents with Crohn's disease will take part in this study for up to 55 weeks (12 months and 3 weeks) plus a follow-up phone call 10 weeks after the last dose of study medication is taken. About 6 children and teenagers will take part from the IWK. Those who complete the 52 weeks of treatment in this study will have the opportunity to continue into an open-label extension study. This extension study will be discussed at a later time.

An open-label study means that you will get adalimumab, not placebo (no active drug) at a known dose.

A double-blind study means that you will get adalimumab but that the dose you receive will not be known to either you or the study doctor. In an emergency, the study doctor can contact the sponsor to find out what your dose is.

The adalimumab is given by subcutaneous injection, which means it is given with a small needle just under the skin.

INDUCTION

At the start of the study, participants will receive an open-label induction dose of adalimumab. An induction dose means a higher than normal dose of study drug in order to start treatment.

If you weigh greater than or equal to 40 kg (approximately 88 lbs) at the Baseline study visit, you will receive an initial dose of 160 mg adalimumab (4 shots of 40 mg) at baseline (Week 0) and 80 mg adalimumab (2 shots of 40 mg) at Week 2. All other doses of study drug will be given as one injection.

If you weigh less than 40 kg (approximately 88 lbs) at the Baseline study visit, you will receive an initial dose of 80 mg adalimumab (2 shots of 40 mg) at baseline (week 0) and 40 mg adalimumab (1 shot of 40 mg) at Week 2. All other doses of study drug will be given as one injection.

BLINDED TREATMENT

These induction doses will be followed by blinded treatment of adalimumab every other week from Week 4 through Week 52. Blinded treatment means that neither you, your parent nor the study staff will know the dose of adalimumab you will be receiving; however, you will get adalimumab and not placebo (no active drug). There are two (2) dosing groups of adalimumab that are being tested in this study- a high dose and a low dose depending on your weight at the Week 4 study visit. You will be selected by chance (like the flip of a coin) and will have a 50% chance of receiving the high dose of adalimumab and a 50% chance of receiving the low dose of adalimumab.

If you weigh greater than or equal to 40 kg (approximately 88 lbs), you will either be receiving 40 mg of adalimumab every other week or 20 mg of adalimumab every other week beginning at Week 4. If at or after Week 12 your Crohn's disease becomes more active or you do not respond to study drug, and you meet certain criteria, the study doctor may be able to change your study medication to weekly injections of the same study drug. If, following 8 weeks of weekly blinded dosing, your Crohn's disease becomes more active or you do not respond to study drug, and you meet certain criteria, the study doctor may be able to change your study medication to open-label (known dose) adalimumab.

If you weigh less than 40 kg (approximately 88 lbs), you will either be receiving 20 mg of adalimumab every other week or 10 mg of adalimumab every other week. If at or after Week 12 your Crohn's disease becomes more active or you do not respond to the study drug, and you meet certain criteria, the study doctor may be able to change your study medication to weekly injections of the same study drug.

Your weight at Week 26 will be used to readjust the dose if your weight has increased from below 40 kg to above 40 kg during the study. If, following 8 weeks of weekly blinded dosing, your Crohn's disease becomes more active or you do not respond to study drug, and you meet certain criteria, the study doctor may be able to change your study medication to open-label (known dose) adalimumab.

If you complete the study, you will have the opportunity to enter into a long-term extension study and receive open–label doses of adalimumab. This will be discussed at a later time.

WHAT WILL I BE ASKED TO DO?

If you agree to be in this study, the following will happen:

Before the study drug is started, your medical history including current and former medications will be reviewed and a medical history specific to any prior exposure to tuberculosis (TB) will be discussed at a Screening visit. You willl have a physical exam, blood tests, urine test, a stool test, electrocardiogram (ECG - a test that studies the electrical activity of the heart), and, if you are a female of child-bearing age, you will have urine and blood tests for pregnancy. If the pregnancy test is positive, participation in the study cannot proceed. Appropriate pregnancy counseling will be provided. You will have a chest X-ray to make sure you have no lung disease and an X-ray of your wrist, which will be used to determine changes in bone development. A tuberculin PPD (Purified Protein Derivative) skin test will be done (this is a test that determines whether or not you have been exposed to tuberculosis or TB). **The PPD must be read within 48-72 hours after receiving it either by study staff, family doctor or Public Health nurse.** If the PPD is positive, indicating that you have been exposed to tuberculosis, you may be asked to take anti-tuberculosis medication for a period of 9 months and would be treated by an infectious disease specialist. You will not be able to receive the first dose of adalimumab until the treatment for TB has begun. You will have an additional chest X-ray at Week 26.

Approximately 9 mls (2 teaspoons) of blood will be drawn at this screening visit. One of the blood tests will be done at the IWK lab; the rest will either be sent right away to ICON Laboratory in Farmingdale, New York or frozen at the IWK and sent at a later date to ICON. The blood collected will only be used to do the tests required and will be destroyed after those tests are completed. All of this testing will be done to be sure that you meet the study entry requirements and that it is safe for you to receive adalimumab. If you do not meet all of these requirements you will not be able to take part in the study. The Screening visit will take about 3 hours.

You may be required to stop certain medications you are currently taking in order to take part in this study. Any previous anti-TNF medication (including adalimumab) with the exception of infliximab is not permitted. You would have had to stop infliximab for a period of at least 8 weeks prior to the Baseline study visit. The study doctor will review your current medications with you and tell you specifically if you must stop using any of the medications you are currently taking.

One to three weeks after the Screening visit, you would return to the clinic for the Baseline visit. Medication use will be reviewed again along with any unusual medical events that may have occurred to you since screening. You will have a physical exam, blood and urine tests and, if you are a female of child-bearing age, a urine test for pregnancy will be done. You will be asked to complete an IMPACT questionnaire. This consists of 35 questions about your

quality of life in relation to Crohn's disease. Your parent will be asked to complete the Work Productivity and Impairment Questionnaire (WPAI). This consists of 6 questions about how your Crohn's disease affects your parent's work life and other activities.

On this Baseline visit, you will receive the first dose of adalimumab. The study nurse will give this first dose. All doses of adalimumab are based on your weight. At this visit, you and/or your parent or other family member will be instructed on how to give the injections. You, your parent or other family member will give the injections with supervision at Week 2 and Week 4. The rest of the injections will be given at home every two weeks for the remainder of the study. The Baseline visit will take about 2 hours.

During the study, you will visit the GI clinic at Screening, Baseline (approximately 1-3 weeks after screening), Week 2, Week 4, Week 8, Week 12, Week 16, Week 20, Week 26, Week 32, Week 40, Week 48 and Week 52- a total of 13 visits. Each study visit will take about 1-½ hours. If you continue into the open-label extension study after Week 52, you will be required to return to the clinic as specified in the extension study's informed consent. This consent will follow at a later date. At all visits you will undergo a physical exam, clinical assessment, and have urine test and blood tests. Approximately 9 mls-17 mls (2-4 teaspoons) of blood will be drawn at each of these visits. At some visits, up to 35 mls (7 teaspoons) of blood will be collected. A total of 200ml (40 teaspoons or 14 tablespoons) of blood will be taken during the whole study. [See the Study Schedule on page 7 for the amount of blood taken at each visit]. A second chest x-ray will be done at Week 26. At Week 52, you will have an additional x-ray of the wrist to assess bone development. At every visit, if you are 13 years of age or older at the baseline visit, you will be required to take a card home and record the number of bowel movements you had, how much pain you are having, and rate your general well being. This diary is to be returned to the clinic at each study visit. You will also be asked to complete a card to record information about any new medications or changes in medication taken on an ongoing basis throughout the study. This card must be returned at each study visit.

At every study visit you will be asked about any side effects you are having, problems you are having which may or may not be related to the study drug and any change in the medications you are taking. If you are greater than or equal to ten years old at the time of Baseline, you will need to complete an IMPACT questionnaire about your health at Baseline, Week 12, Week 26 and Week 52 visits. At every visit, your parent will be asked to complete the WPAI questionnaire. You will also be asked at every study visit to inform the study doctor of any visits you have made to other doctors or hospitals.

At or after Week 12, if you are having a disease flare (worsening of Crohn's disease) or you are not responding to the study medication, you may be switched to <u>weekly</u> dosing of the study drug if the study doctor determines that you meet study requirements.

Following 8 weeks of weekly blinded dosing, if your Crohn's disease becomes more active or does not respond to treatment, and you meet certain criteria, your study doctor may change the study medication to open-label adalimumab.

If you should later have another flare or continue not to respond to study medication while receiving open-label study medication, you may come in to the study doctor's clinic to determine if you can remain on study medication or should be discontinued from the study.

If you are having a disease flare or are not responding between scheduled study visits, you should return to the study doctor for an extra study visit. This extra study visit will consist of physical exam, blood test, urine test and update of any adverse events and medications you have been taking.

If your participation in this study is discontinued early for any reason, we would ask that you visit the study doctor for a final study visit. At that time the study doctor will discuss other study drugs with you and your parent. At this visit your will have a physical exam, blood test, urine test, complete questionnaires and update of any adverse events and medications he/she has been taking, the same as at the Week 52 visit.

If you choose to stop participating in this study or do not continue in the extension study, the study doctor's office will contact you seventy (70) days after the last injection to get information about any ongoing or new side effects you may have had.

You will be provided with the medication and all supplies along with instructions for giving the injections. Both used and unused medication must be returned to the clinic at each visit. You are the only person allowed to take the study medication. The study medication and injection supplies must be kept out of the reach of children and persons of limited capacity to read or understand. Since the medication must be kept cool at all times, your will be provided with a tote bag, cooler and ice packs to transport the medication. A container to dispose of used needles safely will also be provided.

You must not change any of your Crohn's disease medications or start any new Crohn's medications without checking with the study doctor.

During the course of the study, some information from your hospital chart will be recorded on the research charts. You will be given a unique study number on the research records to protect your identity.

The following page contains a chart of the study visits, what is done at each visit and the amount of blood taken each time. The activities marked with an asterisk * are for research purposes only.

*** For research purposes only**

Activity	Screen-ing	Base-line	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 26	Week 32	Week 40	Week 48	Week 52/ Early Term	Unsched-uled visit	70-Day Phone Call
Informed Consent *	X														
Medical/Surgical History	X	X													
Physical Exam	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PPD Skin test *	X														
Chest X-ray *	X								X						
X-ray for Bone Age *	X												X		
ECG *	X														
Blood tests	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Amount of blood taken	2 tsp	6 tsp	3 tsp	3 tsp	3 tsp	2 tsp	4 tsp	2 tsp	5 tsp	2 tsp	2 tsp	2 tsp	5 tsp	2 tsp	
Serum Pregnancy Test *	X														
Urine Pregnancy Test *		X	X	X	X	X	X	X	X	X	X	X	X	X	
Stool test	X														
Urine test	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
IMPACT III Questionnaire *		X				X			X				X		
Unscheduled Outpatient Visits, ER Visits and Hospitalizations Questionnaire *		X	X	X	X	X	X	X	X	X	X	X	X		
Work Productivity and Impairment Questionnaire: Crohn's Disease (WPAI) *		X	X	X	X	X	X	X	X	X	X	X	X		
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X

SUBJECT'S RESPONSIBILITIES:

In order for this study to be successful and give good information about how this drug works in Crohn's disease, it is important that you and your parent do the following:

- Come to the scheduled study visits.
- Take the study medication as instructed and return the used and unused study medication to the doctor's office at each visit.
- Fill out your dosing sheet completely and honestly and bring it to the doctor's office at each visit.
- Fill out the questionnaires honestly.
- You must not change any of your Crohn's medications or start any new Crohn's medications without checking with the study doctor.
- You should not receive a vaccine that is described as "live" while taking adalimumab and for 70 days after their last dose. There is no data on the effects of live vaccines in patients receiving adalimumab. Prior to receiving any vaccination, check with your study doctor.
- You should not receive any enemas or suppositories except if required prior to a routine colonoscopy.
- Tell the study staff of any health problems you are having even if you don't think they are important.
- Tell the study staff if you wish to stop being in the study and come back for the final visits.

If you feel that this study would take too much time, you should not agree to be in the study.

You are the only person allowed to take the study medication. The study medication and injection supplies must be kept out of the reach of children and persons of limited capacity to read or understand.

WHAT ARE THE BURDENS, HARMS AND POTENTIAL HARMS?

The following risks and discomforts were seen in previous adult adalimumab studies. You may or may not have any of these side effects. More than 20,000 patients taking part in rheumatoid arthritis, juvenile idiopathic arthritis, Crohn's Disease, psoriasis, ankylosing spondylitis, psoriatic arthritis, and ulcerative colitis in clinical studies have been treated with adalimumab. The majority of side effects experienced following administration of adalimumab were mild to moderate in severity.

Injection Site Reactions

The most common side effect of both adalimumab and the placebo (no active drug) injections was reaction at the injection site. The most common reactions were redness, itching, bruising, pain, and/or swelling at the injection site. Most injection site reactions were described as mild and usually went away without stopping the drug.

Other Common Side Effects

In the rheumatoid arthritis studies comparing patients receiving adalimumab to placebo (no active drug) the following side effects were more frequent in the adalimumab group and occurred at a rate of >/= 5% (about 1 in 20): upper respiratory tract infection, headache, rash, sinus infection, accidental injury, nausea, abdominal pain, back pain, urinary tract infection, hypertension (high blood pressure) and flu syndrome.

Infection Risk

Infections were among the most common side effects seen with adalimumab. The infections were mostly upper respiratory tract infections (common colds), bronchitis, and urinary tract infections.

Serious infections were also seen with adalimumab but were uncommon. These include: pneumonia, septic arthritis (infected joints), sepsis (infection within the bloodstream), post-surgical infections, cellulitis (skin infections), diverticulitis (infection of the colon), pyelonephritis (infection of the kidney), and opportunistic infections including invasive fungal infections. Other serious infections have also been reported. Serious infections may result in death.

Some patients have developed active tuberculosis (TB) while taking adalimumab. Most of the cases occurred within the first 8 months of taking adalimumab. This may indicate an activation of a previously inactive tuberculosis infection. If you have a history of active tuberculosis, you will not be entered in the study.

You should not start adalimumab if you have any active infection of any kind. If you develop a new infection while on the study drug, the study doctor will follow you closely. If the infection becomes serious, the study doctor may stop the study drug. If you have any symptoms of infection, serious or not, tell the study doctor or research nurse.

Very rare cases of relapse of Hepatitis B virus infection have occurred in patients taking TNF blockers such as adalimumab.

You should not receive a vaccine that is described as "live" while taking adalimumab or for 70 days after the last dose. There is no data available on the effects of live vaccines in patients receiving adalimumab.
Examples of "live" vaccines include: measles-mumps-rubella (MMR), oral polio vaccine, BCG, typhoid, yellow fever, small pox and varicella (chickenpox). Before receiving any vaccination, check with the study doctor or research nurse.

Cardiovascular Risk

There is a possibility that drugs that decrease the action of Tumor Necrosis Factor (TNF) may cause or increase the risk of congestive heart failure. If you have moderate to severe heart failure, you will not be enrolled in this study. Caution must be used in patients with mild heart failure. If you have worsening of symptoms, shortness of breath or swelling of ankles and feet, contact your study doctor immediately. At this time, the role of adalimumab in patients with congestive heart failure is not known. In children who receive adalimumab, the cardiovascular risk is much less than 1%.

Neurologic Risk

There have been cases of nerve demyelination (breakdown of nerve cells) in patients getting adalimumab. An example of nerve demyelination is multiple sclerosis. Symptoms of demyelinating disease include numbness or tingling, problems with vision, weakness in legs and dizziness. It is not known if treatment with adalimumab has caused these side effects. The majority of these patients recovered after stopping adalimumab.
There have been cases of Guillain- Barré syndrome (a rare disorder in which the body's immune system attacks part of the peripheral nervous system) reported in patients taking adalimumab.

Cancer Risk

Adalimumab belongs to a class of drugs called TNF blockers. In clinical studies of all the TNF-blocking agents, more cases of cancer including lymphoma and non-melanoma skin cancer have been observed among patients receiving TNF blockers compared to patients who did not receive these drugs. You should discuss these issues with your study doctor.

Lymphoma is a type of blood cancer affecting the lymphatic system. Patients with rheumatoid arthritis, particularly those with highly active disease, may be at a high risk (many times higher than the normal rate in the general population) for the development of lymphoma. Rare cases of hepatosplenic T-cell lymphoma, another form of lymphoma, have been identified in patients treated with adalimumab. This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. Some of the cases reported for adalimumab occurred in young adult patients with inflammatory bowel disease who were also taking other oral medications, e.g., azathioprine, that can suppress the immune system.

Non melanoma skin cancers, which include basal cell carcinoma and squamous cell carcinoma of the skin, are usually non life threatening if caught early.

The more frequently observed cancers other than lymphoma and non-melanoma skin cancer during the use of adalimumab include cancers of the breast, colon-rectum, uterine-cervical, prostate, ovary, lung, melanoma, and other carcinomas. Some cancers may result in death. In the unlikely event that you develop cancer of the gastrointestinal tract, you will not be able to continue in the study. Appropriate medical care will be provided. In children who receive adalimumab, the cancer risk is much less than 1%.

Allergic Reaction Risk

Allergic reactions such as allergic rash and itching have been observed in approximately 1% of patients taking adalimumab. Serious allergic reactions (e.g., Stevens Johnson syndrome, anaphylaxis, angioedema) that could be life-threatening were seen rarely in people taking adalimumab. Before starting the study drug, you must tell the study doctor about any drug allergies you may have. **You should notify the study doctor right away if you have any allergy**

symptoms such as rash, hives, swelling, itching, shortness of breath, or trouble breathing.

Hematological Risk

Rare cases of blood disorders such as aplastic anemia (low levels of red blood cells), thrombocytopenia (low platelets), leukopenia (low white blood cells) and pancytopenia (low counts of all blood cell types at the same time) have been reported with adalimumab. The relationship of these reports to the use of adalimumab is not known.

Crohn's Disease Risk

There have been isolated reports of intestinal obstruction in patients with Crohn's Disease receiving TNF blocker therapy. Intestinal obstruction can occur in patients with Crohn's disease as a result of ongoing active disease. At this time it is not clear whether the intestinal obstruction seen in patients receiving TNF blocker therapy was due in part to the medication, or as a complication of Crohn's disease. As part of the ongoing study visits we will be watching for any symptoms which might suggest bowel obstruction – and if seen, would investigate further. There have been reports of intestinal perforation in patients with Crohn's Disease taking adalimumab.

Other Adalimumab Risks

Deaths have occurred during treatment with adalimumab. However, the risk of death for those receiving adalimumab is not increased compared to death rates for people of the same age and gender.

Formation of auto-antibodies, antibodies that develop against one's own cells or proteins, have been seen during adalimumab administration. In rare cases, auto-antibody production, joint pain and rash can develop that appear similar to that seen in a disease called lupus erythematosus. In most people these symptoms go away when adalimumab is stopped. Lupus erythematosus may have effects on the internal organs. The role of treatment with adalimumab on the development of autoimmune diseases is unknown.

Rare cases of interstitial lung disease (scarring and/or inflammation of the lungs) have been reported in clinical trials.

A side effect that has been reported since the first regulatory approval and outside of clinical trials is cutaneous vasculitis (inflammation of the blood vessels of the skin).

The most common reasons causing patients to stop taking adalimumab are infections and surgical procedures.

Abnormal laboratory test values that are sometimes seen in patients taking adalimumab include: high cholesterol, elevated fats (lipids) in the blood, blood in the urine, and increased liver enzymes. Increased liver enzymes may indicate liver damage.

Side effects that have been reported since the first regulatory approval include cutaneous vasculitis (inflammation of the blood vessels in the skin) and interstitial lung disease (scarring and/or inflammation of the lungs).

The needle cover of the pre-filled syringe contains latex (dry rubber). If the person who will be giving the injections (you, your child or another family member) is sensitive to latex, please tell the study doctor before the study starts.

Certain medicines should not be used together because an interaction may occur. The use of adalimumab and anakinra (e.g., Kineret) together is prohibited because patients taking anakinra with a TNF blocker such as adalimumab have experienced serious side effects. The use of adalimumab and abatacept (e.g. Orencia) together is not recommended because patients taking the combination may have increased risk of infection and serious infections. Tell the study doctor if you are taking any other prescription or nonprescription (over-the-counter]) medicine.

Your study doctor will be watching you closely for side effects from adalimumab**. It is important that you report any side effect you may have to the study doctor right away.** The study doctor may give you other drugs in order to keep side effects under control. If you, or the study doctor feels that you cannot tolerate the side effects, the study drug may be stopped altogether and you will be withdrawn from the study.

Blood Draw Risks

You may have pain or bruising at the site where the blood is drawn. You may feel faint. An infection at the site where the blood was drawn is possible. Ametop® (freezing cream) can be applied with a sticky patch to the area one hour before the blood is drawn to make it hurt less or not at all.

X-ray Risks

Everyone is constantly exposed to radiation. This comes from many sources, both natural and man-made. More than 2/3 of the radiation we are exposed to exists naturally throughout the universe in the form of cosmic radiation. Man-made radiation comes from sources such as x-rays and self-illuminating products such as signs. The risk of x-ray exposure for the tests required for this study is much less than for a white blood cell scan, a test patients with Crohn's disease in Halifax usually receive.

Reproductive Risks

Girls/Women Who Can Get Pregnant or Are Breastfeeding

You may not take part in this study if you are breastfeeding, pregnant, think that you may be pregnant, or trying to get pregnant as there may be risks to the unborn baby that are not known at this time. If you are a female who is 10 years old or older and/or you have begun menstruating or if you begin menstruating during the trial, your urine will be tested for pregnancy at each study visit. There is no information if adalimumab is safe for breastfeeding or unborn babies of mothers getting adalimumab.

You must avoid getting pregnant in order to take part in this research study. If you are sexually active you must use a method of birth control that is acceptable to you, the study doctor, and the sponsor. You must continue to avoid pregnancy for 150 days (5 months) after the last dose of study drug. Examples of acceptable forms of birth control include condoms, sponge, foam, jellies, diaphragm, intrauterine device (IUD), and oral, parenteral, or intravaginal contraceptives. If you use an oral contraceptive, or other type of hormonal contraceptive such as skin patch injection, or implant, you must have been using the contraceptive for a minimum of 12 weeks prior to beginning the study medication. The study nurse or doctor will discuss birth control with you before and during the study, as appropriate.

It is important for you to tell the study doctor at once if you become pregnant or think that you might be pregnant while in the research study. If you get pregnant, you will be asked to stop taking part in the study and appropriate counseling will be offered to you. Information regarding the pregnancy, and the outcome of the pregnancy will be collected as part of this study unless consent for further contact has been withdrawn. You may also be asked questions about the pregnancy and the baby even after the study is over.

Male contraception:

You should not father a child while in this study or for 150 days (5 months) after the last study treatment.

The effects of adalimumab on human sperm are unknown. Males must discuss contraception methods with the study doctor and use contraception while on this study. If you think you may have fathered a child while in this study, you should tell the study doctor right away.

Questionnaires

In the unlikely event that you or your parent becomes upset answering the WPAI or the IMPACT questionnaire, study staff will be available to help you.

Unknown Risks

You might have side effects or discomforts that are not listed in this form. Some side effects may not be known yet. Tell the study doctor or study staff right away if you have any problems. You and your parent will be informed of any new findings or side effects that may affect your decision to stay in the study.

WHAT ARE THE POSSIBLE BENEFITS?

Taking part in this study may be of no help to you personally. No one can predict whether you will respond to this study drug or whether you will gain benefit from it. It is possible that your Crohn's disease will improve while you are taking the study medication. Your condition may not improve or may worsen while participating in this study.

The information that is gained during this study may be helpful to others.

WHAT ALTERNATIVES TO PARTICIPATION DO I HAVE?

You do not have to take part in this study. You will receive the same level of care whether or not you choose to take part. If you choose not to be part of this study, there are other treatment options available.
Some possible treatments may include drugs already approved for Crohn's disease such as corticosteroids, methotrexate, 6-MP, Imuran, antagonists of tumor necrosis factor (TNF) such as infliximab, and other experimental drugs. You can discuss the risks and benefits of these treatments and any other alternative treatments that may be available with the study doctor. These treatments may potentially benefit your Crohn's disease. Please speak to the study doctor to review each of the alternative treatments to fully understand the potential adverse events, side effects or risks that may be associated with each specific treatment.
Not participating in this research study is an option. Not participating will not affect the care you receive at the IWK.

CAN I WITHDRAWAL FROM THE STUDY?

You are free to withdraw from this study at any time without affecting the care you receive or the care your family will receive at the IWK.
As well, the study doctor or sponsor can take you off the study drug and out of the study if:

- The study drug isn't working
- Your health gets worse
- You are unable to meet the study requirements, such as returning for follow-up visits
- For any other reason that the study doctor believes is in your best interest.
- Sponsor decision

If you withdraw permission for any reason after starting in the study, we will not collect any further information about you. However, study information that has been collected and entered in the study will not be withdrawn.

If you choose to discontinue your participation in this study, you should first notify the study doctor before stopping the study drug. You will then be asked to make a visit to the study doctor within two (2) weeks of the last dose of study medication for an early withdrawal visit in order to check for adverse events or side effects that may have occurred from the study medication. At this early withdrawal visit you will complete those assessments/tests as described in the study schedule. The study doctor will also discuss other treatments with you at this visit.

You may cancel permission to take part in this study at any time by contacting the study doctor at the address below or by calling the Research Nurse at 902-[redacted]

Dr. Anthony Otley
[redacted]
IWK Health Centre PO Box 9700
Halifax, NS B3K 6R8
Phone [redacted]

WILL THE STUDY COST ME ANYTHING AND, IF SO, HOW WILL I BE REIMBURSED?

Given the severe nature of your disease, frequent clinic visits would be part of the usual care you would receive. Since two of the study visits are considered "extra", that is, not part of usual care, you will be compensated $30.00 per visit ($60.00 total), payable at the end of the study. If you discontinue participation in the study for any reason, you will be paid $30.00 for the "extra" study visits attended.

The study drug and all examinations, procedures and tests done solely for the purposes of this study will be provided free of cost to you or your parents. The costs of your regular treatment, which is not directly associated with this study, will be your responsibility or the responsibility of your health insurance company or government program. At the end of the study neither the study sponsor, nor its affiliates, has to supply the study medication for further treatment. At the present time, adalimumab is not available for purchase.

ARE THERE ANY CONFLICTS OF INTEREST?

The researchers do not have any financial interest in the sponsor, Abbott; however, the study doctor and the institution are being compensated for the cost of conducting the study. Funds received from this study will be used by the study doctor to do further Inflammatory Bowel Disease research.

WHAT ABOUT POSSIBLE PROFIT FROM COMMERCIALIZATION OF THE STUDY RESULTS?

Your participation may contribute to the creation of new diagnostic tests, new medications or other treatments that may have commercial value. However, your participation in this study will not entitle you or your parents to a share in future economic benefits. During the study, blood may be taken to assess your medical care or for research. Abbott Laboratories will own the rights to any inventions that result from any tests performed on this blood.

HOW WILL I BE INFORMED OF STUDY RESULTS?

The results of this study will be communicated directly to you, if you wish. However, these will not be your individual results but those of the research study in general. Once the study is completed, a written summary of results can be sent to each participant and their family. You can indicate on the signature page of this consent if you wish to be informed of the results.
As well, this research will be discussed at an Annual IBD Information Night session. These evenings are held each year to allow the IBD Team to provide information of clinical and research interest to patients and families.

ONCE THE RESEARCH IS COMPLETE WILL THE DRUG BE AVAILABLE TO ME?

After the study is completed, there will be an open-label extension study for those who wish to continue taking the study drug. There will be a separate consent form for the extension study and this will be discussed at a later time. Adalimumab is available by prescription.

HOW WILL MY PRIVACY BE PROTECTED?

We will try to keep your personal records confidential and private, but we cannot guarantee absolute confidentiality.

The following groups may look at your research records to monitor their quality or study the data:

- *Health Canada and other regulatory agencies*
- *Abbott Laboratories (the study sponsor) or their agents or contractors*
- *IWK Research Ethics Board*

Except for the above situations, your name and all other personal data will be kept confidential and will not be made publicly available, unless disclosure of this information is required by law. By signing this form, you authorize this access to your research records.

Any information that leaves the Health Centre will not have your name on it, but will instead be identified by a unique study number. The information collected as part of the study may be transferred to these organizations electronically but your identity will be protected. If the study is described in a medical journal, report or presentation, you will not be identified.

The study physician will inform your family doctor that you are taking part in this study.

You have the right to request access to your personal information through the study doctor and to correct any inaccuracies that might exist. You have the right to see and make a copy of your study records as allowed by applicable law. You may ask to see your study records by requesting such records from the study doctor. However by signing this form, and in order to ensure the scientific integrity of the study, you agree that you may not be able to review or make a copy of some of your records related to the study until after the study has been completed. The information you would not be able to find out is the blinding (which dose of study drug you received, if that information is known) and the case report forms that are completed at each study visit. You would be able to review all other study information.

Study reports will be stored in a locked area and will be kept for a minimum of 25 years as required by Health Canada. During this time, you or any of the groups listed on the previous page, would be able to see your study records by contacting the study doctor. After that, they would be destroyed.

This consent to disclose your personal health information has no expiration. This means that information collected for research may need to be accessed after the study is done in order to verify certain data. It is not possible to determine how long after the study is completed this access would be needed.

IN CASE OF RESEARCH RELATED INJURIES

If you become sick or injured as a result of the study, you will be provided with needed medical care at no cost to you, your parents or the health care system. Abbott Laboratories will pay for all reasonable medical costs of treating an illness or injury caused by the study drug or a study procedure provided you have followed the directions of the study doctor.

NEW INFORMATION

You will be informed in writing and asked to sign a new (revised) consent form if new information becomes available that might affect your willingness to continue participation in this study.

RESEARCH RIGHTS

Taking part in this study is voluntary. You may choose not to take part in the study, or choose to leave the study at any time. The quality of your medical care will not change should you decide not to take part in the study or if you decide to leave the study early.

Your signature on this form will show that you have understood to your satisfaction the information about the research study and that you agree to co-operate fully with the supervising doctor.

By signing this document, you are not waiving any of your legal rights, nor are you releasing the investigator, institution or sponsor from their legal and professional responsibilities.

If you have any questions at any time during or after the study about research in general, you may contact the Research office at the IWK Health Centre at 902-[redacted] Monday to Friday between 9 am and 5 pm.

CONTACT PERSON

If you have any questions or concerns following your enrollment in this study or if at any time you feel you have experienced a study-related injury or reaction to the study medication, between 8am and 4pm Monday to Friday you may contact the GI Research Nurse, [redacted], at [redacted] or you may contact Dr. Otley at [redacted] In case of an emergency, you may contact the gastroenterologist on call at the Health Centre by calling [redacted] and asking for him to be paged.

Study Title: The Safety and Effectiveness of Adalimumab in Children and Adolescents with Moderate to Severe Crohn's Disease

PARTICIPANT ID: _ [redacted] **PARTICIPANT INITIALS: _** [redacted]

PARTICIPANT NAME:_____ [redacted] **_____**

Participant Consent

I have read or had read to me this information and consent form and have had a chance to ask questions which have been answered to my satisfaction before signing my name. I understand the nature of the study and I understand the potential risks or reactions. I understand that I have the right to withdraw from the study at any time without the need to justify my decision and without affecting my care in any way. I have been informed about the compensation and/or treatment available in the event of trial-related injury. I have received a copy of this information and consent form for future reference. I freely agree to participate in this research study.

_[redacted]_____ _[redacted]_____

Name of Participant (Print) Signature of Participant

Date: _[redacted]_ Time: _[redacted]__

I wish to receive a copy of the study results when they are available.

Yes [redacted] No [redacted] Address_[redacted]

STATEMENT BY PERSON PROVIDING INFORMATION ON STUDY

I have explained the nature and demands of the research study and judge that the participant named above understands the nature and demands of the study.

Name (Print) _[redacted]__Position [redacted]

Signature: _[redacted]_____Date: [redacted]_ Time: _____

STATEMENT BY PERSON OBTAINING CONSENT

I have explained the nature of the consent process to the participant and judge that they understand that participation is voluntary and that they may withdraw at any time from participating.

Name (Print) _[redacted]____Positi[redacted]

Signature: _[redacted]_____Date: _[redacted] Time: ____[redacted]