Serial Response and Biomarker-Guided Steroid Taper for Children With GVHD

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Informed Consent to Participate in Research

MAGIC 4

Serial Response and Biomarker-Guided Steroid Taper for Children with GVHD

Your Name: _____

Principal Investigator:

Insert local PI information with site address

Sponsor: This study is sponsored by The Gateway for Cancer Research, through Mount Sinai Acute Graft-versus-Host Disease International Consortium (MAGIC)

The ethics of this study have been reviewed and approved by the National Marrow Donor Program Institutional Review Board

Your study doctor or nurse will review this **Consent Form** with you, including:

- ✓ The purpose of the research
- ✓ Possible risks and benefits
- ✓ Other options available to you
- ✓ Your rights if you join the study

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1. Study Overview

We invite you to join this clinical trial, also known as a research study. You are being asked to join because you have newly diagnosed low risk acute Graft-Versus-Host-Disease (GVHD). Acute graft-vs-host disease (GVHD) occurs when donor immune cells attack the healthy tissue of a bone marrow or stem cell transplant patient. The most common symptoms are a skin rash, nausea, vomiting, diarrhea, and/or jaundice. The standard treatment for GVHD is to suppress the activity of the donor immune cells using steroid medications such as prednisone. Although most GVHD, especially in children and young adults, responds well to treatment, sometimes (around 1/3rd of the time) there is either no response to steroids or the response does not last. In those cases, the GVHD can become dangerous and even life-threatening. Unfortunately, doctors cannot predict who will have a good response to treatment based on initial symptom severity or even early response to steroids. As a result, nearly all children and young adults are treated with long courses of high dose steroids even though that means many patients receive more treatment than they probably need. Steroid treatment can cause short-term complications like infections, weight gain, high blood sugar, high blood pressure, muscle weakness, depression, anxiety, and problems sleeping and long-term complications like bone damage, cataracts in the eyes, and decreased growth. The risk of these complications increases with higher doses of steroids and longer treatment. It is important to find ways to decrease the steroid treatment in patients who do not need long courses.

We're doing this study to find out how many subjects respond well to lower steroid dosing and if they develop fewer complications. This will be assessed weekly by both your clinical response and a blood test (GVHD biomarkers) developed by the researchers of this study.

This study will take about 3 years to complete and will include 50 people.

If you join, you'll:

- Be in the study for up to 1 year
- Be given oral prednisone for treatment of your GVHD, and the study team will provide information regarding how to change your dose for the first 4 weeks of your treatment. If you cannot take oral medications then you can receive intravenous versions of prednisone.
- Be asked to complete 4 surveys about your quality of life
- Be asked to provide blood samples

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Some possible risks and benefits of joining the study include:

Possible Risks: You have side effects from the study drug, or your acute GVHD does not get better

Possible Benefits: Your acute GVHD may get better

If you do **not** join the study, you have other treatment options, such as:

- Corticosteroids (for example, prednisone or methylprednisolone) may be given even if you are not on this trial.
- Participation in another clinical trial. Ask your doctor if this may be an option for you.

Key points:

- Being in any research study is your choice.
- You may or may not benefit from being in the study. Knowledge gained from this study may help others.
- If you join the study, you can quit at any time. If you decide to quit the study, it will not affect your care at [name of facility or institution].
- Ask the study staff questions about anything you do not understand, or if you would like more information. You can ask questions now or any time.
- Take time to talk about the study with your doctor, study staff, and your family and friends. It is your choice to be in the study. If you decide to join, please sign the end of this Consent Form. You'll get a copy to keep. No one can force you to join this study.

2. Study Purpose

We're doing this study to find out how many subjects respond well to lower steroid dosing and if they develop fewer complications. This will be assessed by both the clinical response and a blood test (GVHD biomarkers) developed by the researchers of this study. They found that pediatric patients who have low GVHD biomarkers at the start of treatment and for the first two weeks of treatment have a very high response rate to steroids (96%) that lasts. In this study, we will decrease the amount of steroids used to treat GVHD patients who are expected to respond very well. We will do this by starting at a lower dose of prednisone and reducing the dose rapidly

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to see if the biomarkers stay low and the subject is responding. If the GVHD symptoms get worse or if the biomarkers increase, which may occur in some subjects we will increase the steroid dose

We also want to study how the treatments affect your quality of life. We will use surveys to obtain the patient's own assessment of their quality of life (down to age 8) and a parental proxy survey for patients ages 5 to 17. Quality of life means how well you can do your normal everyday activities. We hope that the results of this research will help us develop treatments for GVHD that are safer than currently available

3. Study Treatment and Tests

Before Your Treatment

You'll need to have several tests to see if you can be in the study. Most of these tests are part of your regular care. They would be done even if you decide not to join this study. The tests include:

- Physical exam (including height and weight)
- GVHD assessment
- Blood tests including blood cell counts and liver function
- Patient reported outcome (PRO) surveys (questions about physical activity, feeling tired and mood) will be administered at day 0. Due to timing of enrollment, this might be conducted at the time of consent and prior to eligibility being confirmed.
    - If you end up not going on study, this survey will be destroyed.

During the Study

If you join the study, here's what will happen:

- You will be given oral prednisone for treatment of your GVHD, and the study will provide information regarding how to change your dose for the first 4 weeks of your treatment. If you cannot take oral medications, they can receive intravenous versions of prednisone**.** The dose of prednisone will vary based on your response. Your study doctor will discuss this with you.
- Five mL (1 teaspoon) of blood will be collected from you after GVHD has been diagnosed to confirm study eligibility and before any treatment has begun. Additional

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blood samples will be sent weekly through day 28 of the study (4 samples), and again if your GVHD gets worse.

- Patient reported outcome (PRO) surveys (questions about physical activity, feeling tired and mood) will be administered at day 0 (if not already given), day 28, three months, and six months.

- During the first 4 weeks, you will be evaluated at least weekly for assessment of your GVHD. Subjects will also be evaluated at study day 42, 56, 90, 180, 1 year and at the time of GVHD flares. Telehealth visits are permitted when in person visits are not feasible. Study visits will typically occur during routine clinic visits to monitor your recovery from the transplant

- Because this project involves the use of medications, it is necessary that we make a note of your participation in the electronic medical record. That way anyone treating you will be aware of your participation and may be able to avoid any unfortunate outcomes that could arise if your research participation were unknown.

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Table 2. Timeline of Study Tests

	DAYS											
Assessments	**Screening**	**Study Day 0**	**7**	**14**	**21**	**28**	**42**	**56**	**90**	**180**	**365**	**GVHD Flare**
Windows	**Before you are on the study**	**Start of prednisone (or equivalent) therapy tart**	*+/- 2 days*	*+/- 2 days*	*+/- 2 days*	*+/- 2 days*	*+/- 2 days*	*+/- 3 days*	*+/- 7 days*	*+/- 14 days+/- 14 days*	*+/- 14 days*	*+/- 3 days*
Eligibility Review: Health history and physical exam	X											
Concomitant Medication Review	X	X	X	X	X	X	X	X	X			
Informed consent	X											
Serum chemistry	X											
Acute GVHD assessment	X	X	X	X	X	X	X	X	X	X	X	X
Height and Weight	X					X		X	X	X	X	
Chronic GVHD evaluation										X	X	
Quality of life surveys (Patient and parent proxy)		X*				X			X	X		
5 ml serum (Correlative Studies)	X		X	X	X	X						X

*Day 0 PRO survey might be administered at the time of consent

Serum samples will be banked for correlative studies.

Stopping Treatment

We'll stop the treatment if:

- You need a medical treatment not allowed in this study.
- The study doctor decides that it would be harmful to you to stay in the study.
- You're having serious side effects.
- You cannot keep appointments or take study drugs as directed.

The study is stopped for any reason.

Seeing your Research Results

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Your doctor may not share with you your research results. Your doctor will share any results with you if they show that you need new treatment or need to change your treatment. If you'd like to see specific results, tell your doctor.

Timeline and Participants

This study will take about 3 years to complete and will include 50 people.

4. Risks and Benefits

Possible Benefits

Taking part in this study may or may not make your health better. If it works for you, you may experience fewer infections, less weakness, and better mood and sleep. The information from this study could help future patients with GVHD.

Possible Risks

You may have side effects during the study. Side effects can range from mild to severe. Your health care team may give you medicine to help with certain side effects, like an upset stomach. In some cases, side effects can last a long time or may never go away.

Risks of Medicines

Prednisone

The standard treatment for GVHD is prednisone. This study hopes to decrease the total dose and duration of prednisone treatment. You will be closely monitored for side effects of prednisone. Please review the list of common and serious side effects below:

Likely, some may be serious (May happen in 20% or more patients)	**Less Likely, some may be serious** (May happen in less than 20% of patients, but more than 3%)	**Rare and serious** (May happen in 3% or fewer patients)
• Acne • Difficulty controlling blood sugar levels • Difficulty sleeping • High blood pressure	• Fragile bones, which may cause bone fractures • Headache • Increased pressure in the eye causing eye pain and	• Pressure in the brain (which may cause headache, nausea, confusion, and decreased alertness)

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• Inadequate function of adrenal gland which can cause the inability to mount a stress response • Increased appetite, weight gain • Infection and delayed healing of wounds • Low potassium in the blood which can lead to weakness, fatigue, muscle cramps and spasms, and heart palpitations • Mood swings • Seizures or spasms • Swelling of the face and body • Thin and fragile skin • Ulcers in the stomach, which may cause bleeding	blurred vision and could lead to glaucoma which can result in blindness • Inflammation of the pancreas (upper abdominal pain, nausea, vomiting, elevated enzymes in blood tests) • Muscle loss or weakness • Rash • Slow growth (for example, height) • Tendon rupture	

Prednisone may slow growth and development in children and young adults. Your doctor will watch your growth carefully. Prednisone can also weaken the immune system. Notify your doctor right away if you are concerned that you have a fever or could be developing an infection.

Prednisone may increase the risk that you will develop osteoporosis (bones become weak). Talk to your doctor about the risks of taking prednisone and about things that you can do to decrease the chance that you will develop osteoporosis. Talk to your doctor about the risks of taking prednisone.

Prednisone may cause other side effects. Call your doctor if you have any unusual problems while you are taking this medication.

Subjects eligible for this trial have biomarker proven low risk GVHD. These subjects have a

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very high chance of responding to standard therapy with prednisone. Due to the significant side effects seen in patients taking prednisone, the goal of this study is to reduce the dose and duration of steroid treatment. It is possible that decreasing the prednisone dose may decrease the chance of the GVHD responding to treatment, which may require increasing the dose of prednisone or possibly having to add additional medications to treat the GVHD. The study will closely monitor the number of subjects that fail to respond to treatment, and if the number is higher than expected the study will be closed and subjects and their families still receiving treatment will be notified right away

Other Treatments or Medicines

Some medicines react with each other, so it's important to tell the study doctor or staff about any other drugs, treatments, or medicines you're taking. This includes non-prescription or over-the-counter medicines, vitamins, and herbal treatments.

It is also important that you tell the study staff about any changes to your medicines while you're in the study.

Risks of Blood Draws

There are no major risks with blood draws. A blood draw can hurt a little and may cause a bruise. On rare occasions, people feel lightheaded or faint. Only trained people will draw your blood.

The risks associated with data collection and submissions to the MAGIC database.

This risk is primarily the potential loss of confidentiality of patient-related information. To protect you from this risk their information will be recorded using a 9-character code that identifies your transplant center and a unique number. Only your transplant center will be able to link you personally to the clinical data submitted. The database will not record your name or any other personally identifiable information.

Reproductive Risks

The drugs used in this research study may affect your ability to have children. If you or your partner become pregnant during the study, the drugs used may hurt your baby. Doctors don't know all of the possible risks to your baby if you or your partner become pregnant during the study.

You should always use a form of birth control that is best for you if you don't want to have a baby.

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Tell your doctor right away if you or your partner become pregnant during the study. Your doctor will talk with you about the risks to your unborn child and your options. If you become pregnant, you [will/may/ will not] be asked to leave the study.

Surveys

There are very few risks with taking the study surveys. The main risk is that your confidentiality could be lost. The study team will do everything it can to keep your answers confidential.

Also, some of the questions or topics may upset you. If this happens, your doctor can connect you with a counselor or trained support specialist, if needed.

Unforeseen Risks

Other new risks might appear at any time during the study. These risks might be different from what is listed in this Consent Form. There may be some unknown or unanticipated side effects from this treatment. The study team will do everything they can to keep you safe and lower your risk of side effects.

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

5. Your Rights to Withdraw, Ask Questions, and Seek Other Treatment

Being in this study is your choice. You can choose **not** to be in this study or leave this study at any time. If you choose to not join or leave this study, it won't affect your regular medical care in any way. You will still receive treatment for your GVHD from your doctor. If at any time you are considering leaving the study, talk to your study doctor about your health and safety. If you decide to leave this study after taking the study treatment, or your doctor asks you to leave for medical reasons, you will be asked to come back to the doctor's office for tests for your safety. Even if you leave the study, the information collected from your participation will be included in the study evaluation, unless you specifically ask that it not be included.

If you decide to stop being in the research study, please contact the Principal Investigator or the research staff. You may also withdraw your permission for the use and disclosure of any of your protected information for research.

Even if you withdraw your authorization, the Principal Investigator for the research study may still use the information that was already collected if that information is necessary to complete the research study. Your health information may still be used or shared after you withdraw your authorization if you have an adverse event (a bad effect) from participating in the research study.

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If you decide to withdraw your permission to use your collected blood that you had previously agreed to allow the researchers to use, the samples will be removed from consideration for use in any future study and be destroyed. Please contact the Principal Investigator or the research staff if you decide to withdraw your permission to continue using your blood samples.

If at any time you are considering leaving the study, talk to your study doctor about your health and safety.

You have the right to ask questions about the study at any time. If you have questions about the study, please contact:

[Insert contact details for Principal Investigator or study team]

If you want to talk with someone not directly involved in the study, or have any complaints or questions about your rights as a research participant, you may contact:

NMDP Institutional Review Board Administrator at: 1 (800) 526-7809

You must tell [insert name of Principal Investigator] if you decide to leave the study.

Withdrawal without your permission

The study doctor, the sponsor or the institution may stop your involvement in this research study at any time without your permission. This may be because the research study is being stopped, the instructions of the study team have not been followed, the investigator believes it is in your best interest, or for any other reason. If specimens or data have been stored as part of the research study, they too can be destroyed without your permission.

If you choose not to join, other options are available. Your study doctor will talk with you about your options. If you decide not to join this study, your medical care will not be affected in any way.

Your other choices may include:

- Corticosteroids (for example, prednisone or methylprednisolone) may be given even if you are not on this trial.
- Participation in another clinical trial. Ask your doctor if this may be an option for you

Every treatment option has benefits and risks. Talk with your doctor about your choices before you decide if you will be in this study.

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6. New Information Available During the Study

During this study, the study doctors may learn new information about the [treatment/drug] or the risks and benefits of taking part in the study. If they learn new information, they'll tell you as soon as it's available.

The new information may mean that you can no longer participate in the study, or you may not want to continue. If this happens, the study doctor will stop your participation and offer you all available care to meet your health care needs.

7. Privacy, Confidentiality, and Use of Information

Your privacy is very important to us. The study doctors, study sponsor, and other groups with access to your study-related medical information will do everything they can to protect it. The study doctors can protect your records if there is a court case. However, some of your medical information may be shared if required by law. If this happens, the study doctors will do their best to make sure that any information that goes out to others will **not** identify you.

Your confidentiality is one of our main concerns. We will do our best to make sure that the personal information in your medical record is kept confidential (private). However, we cannot promise total privacy.

To make sure the study is running ethically, some government agencies or other groups may need to access part of your medical records. For this study, those groups include:

- [Institution]
- U.S. government agencies that are responsible for overseeing research such as The Food and Drug Administration (FDA) and the Office of Human Research Protection (OHRP)
- U.S. government agencies that are responsible for overseeing public health concerns such as the Centers for Disease Control (CDC) and federal, state, and local health departments
- The Tisch Cancer Institute Data and Safety Monitoring Board (DSMB),
- The NMDP Institutional Review Board (IRB) responsible for this study
- MAGIC Data Coordinating Center
- Study investigators

If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

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Study information may also be used for research in the future. These projects could be related to your disease or similar diseases, or development of the study drug.

Blood or tissue taken during the study may be used for future research. If the study team does this, the blood or tissue will not be attached to you or your name in any way and results of the research done with these samples will not be returned to you.

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

You will **not** be able to access your study results before the study is done. This helps keep the study results accurate and trustworthy.

When the study is complete, you can ask your study doctor for your health information from the study. **By signing this Consent Form, you agree to ask for your results only after the study is done.** You will still have access to your regular medical records.

8. Blood Samples for Future Research

Your blood samples will be stored indefinitely for future GVHD-related research. This blood will be processed in the MAGIC central lab at Mount Sinai and stored in a freezer. These samples will be used in future research to address scientific questions which are important to the biology of GVHD. The samples and/or data collected from you as part of this study may be used for commercial profit and there are no plans to share any profits from such products with you. On occasion, we may send some of these samples to investigators at a different center who are working together with us on research studies but not participating in the MAGIC consortium. These samples will not contain information that will be linked to you.

The samples may be depleted or destroyed without your consent and the samples may be used after your death without further consent.

The data to be collected is usual clinical information recorded during bone marrow transplant care. This information will be stored in an electronic, password secured database for at least 10 years after transplantation or until you withdraw from the study.

9. Leaving the Study

You can choose to leave the study at any time.

You may also be told to leave the study for reasons such as:

- You don't meet the study requirements.

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- You need a medical treatment not allowed in this study.
- The study doctor decides that it would be harmful to you to stay in the study.
- You're having serious side effects.
- You become pregnant.
- You cannot keep appointments or take study drugs as directed.
- The study is stopped for any reason.

Even if you leave the study, the information already collected from you will be included in the study evaluation. If you don't want your information to be used, you **must** let your study doctor know.

10. Cost and Reimbursement

You will not be paid for joining this study. You will not be paid or reimbursed for any extra expenses (such as travel, meals, or loss of income) from your participation in this study. You may have some of these extra expenses regardless of whether you participate on this study or not.

Most of the visits for this study are standard medical care for patients with low risk acute GVHD and will be billed to your health insurance company. You and/or your health insurance company will need to pay for some or all of the costs of standard medical treatment in this study.

Some health insurance plans will not pay for costs of care when you take part in a research study. Check with your health plan or insurance company to find out if they will pay.

You or your health insurance company will not be charged for extra tests or research costs for this study. These include:

- Quality of life assessments
- Blood samples for research

For questions about your costs, financial responsibilities, and/or health insurance coverage for this study, please contact /Hospital/ Financial Counselor at / Number/.

Physical Injury as a Result of Participation
Tell your study doctor or staff if you think you've been hurt because of being in this study. You'll get medical treatment if you're hurt as a result of this study. You and/or your health insurance company will be charged for this treatment. The study sponsor will not pay for medical treatment as a result of unintended injury.

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In case of injury resulting from this study, you don't lose any of your legal rights to seek payment by signing this form.

11. Disclosure of Financial Interests

Researchers sometimes get paid for consulting or doing work for companies that produce drugs, biologics or medical devices. If you have questions regarding industry relationships, you are encouraged to talk to the Principal Investigator at your site or study team member.

Dr. John Levine (the overall Study Principal Investigator) and Dr. James Ferrara (an overall Study Co- Investigator), who are located at the study's central site, Icahn School of Medicine at Mount Sinai Hospital in New York, are named co-inventors on a patent for Acute GVHD Biomarkers. This patent is filed through the University of Michigan and licensed to Viracor (a diagnostic laboratory, which performs testing for inflammatory markers, associated with graft-versus- host disease (GVHD)). Dr. Ferrara and Dr. Levine receive royalty payments from the University of Michigan for this patent.

In addition, Dr. Ferrara and Dr. Levine are named co-inventors on a patent for biomarkers to predict GVHD prior to onset. This patent is filed through the Icahn School of Medicine at Mount Sinai and licensed to Viracor. The medical school has received payments related to this patent and Dr. Ferrara and Dr. Levine are entitled to a portion of these payments. Dr. Ferrara also receives financial compensation as a consultant for Viracor.

If you have questions regarding paid relationships that physician/researchers may have with industry, we encourage you to talk with your study team for more information.

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12. Health Insurance Portability and Accountability Act 1 (HIPAA) Authorization to use health information for research

Your local study hospital will give you a separate form with information about the Health Insurance Portability and Accountability Act 1 (HIPAA).

TITLE: MAGIC-4 Serial Response and Biomarker-Guided Steroid Taper for Children with GVHD

- I have read and understood this Consent Form. The purpose and description of the research study has been explained to me.
- I have had the chance to ask questions, and understand the answers I have been given. I understand that I may ask questions at any time during the study.
- I freely agree to be a participant in the study.
- I have had the chance to discuss my participation in this research study with a family member or friend if I choose.
- I understand that…
    - I may not directly benefit from taking part in the study.
    - My name and personal information will not be identified even if information gained during the study is published.
    - I can leave this study at any time, and doing so will not affect my current care or prevent me from receiving future treatment.
    - I will be given a copy of this signed consent form.
    - I do not give up any legal rights by signing this form.

_____ _____

Participant Name (or Parent/Guardian) Date (MM/DD/YYYY)

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Participant Signature (or Parent/Guardian) Date (MM/DD/YYYY)

Physician certification

I certify that I have provided a verbal explanation of the details of the research study, including the procedures and risks. I believe the participant has understood the information provided.

Counseling Physician Name Date (MM/DD/YYYY)

Counseling Physician Signature Date (MM/DD/YYYY)

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Interpreter certification (if needed)

I certify that I have provided an accurate interpretation of this consent form. I believe the participant has understood the information provided.

Interpreter Name	Date (MM/DD/YYYY)
Interpreter Signature	Date (MM/DD/YYYY)

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