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Randomized feasibility study of discontinuation versus continuation of immunosuppressive therapy (IST) in patients with chronic Graft Versus Host Disease (GVHD) (Protocol 9962)

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Protocol Synopsis

Title	Randomized feasibility study of discontinuation versus continuation of immunosuppressive therapy (IST) in patients with chronic Graft Versus Host Disease (GVHD)
Short Title	Functional Tolerance after Allo HCT
Study Design	Randomized prospective study
Study Objectives	Primary Objective. Assess feasibility of enrolling and randomizing patients with chronic GVHD to discontinuation versus continuation of IST. Secondary Objectives. - Assess feasibility of enrolling and randomizing patients who are not local, and evaluate the quality of data received for those patients. - Assess whether prolonged IST decreases the need for pulses of high dose IST. - Evaluate the effect of prolonged IST on chronic GVHD manifestations and severity, risk of relapse, infection and organ toxicity.
Study Endpoints	Primary Endpoints. - Number of patients enrolled on the study (signed consent) in 2 years Secondary Endpoint. - Successful randomization of patients - Compliance with treatment and data collection as outlined in the protocol - Rate of IST resumption (discontinuation arm)/increase IST dose (continuation arm) by 12 months after randomization - New chronic GVHD manifestations and/or worsening of existing manifestations, recurrent malignancy by 12 months after randomization, grade $\geq$ 3 infections, and grade $\geq$ 3 organ toxicity.
Accrual Objective	40 (20 patients on each arm)
Study Duration	2 year accrual period; 12 month active follow-up after randomization; Long term annual follow up via chart review.
Stopping Rules	Accrual of less than 12 patients in the first year
Treatment Description	IST continuation for 9 months on the continuation arm. Taper IST to off as planned in the discontinuation IST arm.
Inclusion Criteria	1. Prior allogeneic stem cell transplant, with any graft source, donor type, and GVHD prophylaxis.

	2. On only one systemic immunosuppressive agent for chronic GVHD with a plan to stop all systemic IST. Hydrocortisone or prednisone continued for treatment of adrenal insufficiency is not considered a systemic IST. 3. No evidence of malignancy at the time of enrollment. 4. Agreement for evaluation at the transplant center at the time of study enrollment, and then every 3 months at the transplant center or by local provider for 12 months after randomization 5. Agreement to be contacted by phone or e-mail for health status evaluation for up to 3 years 6. Signed, informed consent
Exclusion Criteria	1. Inability to comply with study procedures 2. Pregnancy

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1. Background and Rationale

Patients who received allogeneic hematopoietic cell transplantation (HCT) typically require administration of immunosuppressive treatment (IST) for at least 6 months in order to prevent or treat graft-versus-host disease (GVHD). GVHD is the most serious and common complication of allogeneic HCT. Significant acute GVHD occurs in 20-50% of patients,(1-3) and chronic GVHD occurs in 30-60% of patients who survive more than 100 days after transplantation.(3, 4) Duration of IST is typically prolonged once patients develop GVHD. Particularly, duration of IST in patients who have chronic GVHD is reported to exceed 2-3 years.(5, 6) While IST is important to reduce mortality and morbidity associated with GVHD, it may increase risks of infection, recurrent malignancy and secondary malignancy.(7)

“Immunologic tolerance” may be defined as the absence of immune-mediated injury when immunosuppressive medications are no longer given. Unlike solid organ transplantation,(8) many patients after allogeneic HCT can achieve sufficient “functional” tolerance even after development of GVHD, and can eventually stop all IST permanently without developing active manifestations of GVHD. However, many patients, especially those with chronic GVHD, develop GVHD exacerbation and require resumption of IST. Currently, there are no clinical or biological predictors for successful IST discontinuation, and management of chronic GVHD patients consists of repeated attempts to taper and stop IST.

A recent retrospective evaluation of 250 adult patients who received systemic treatment for chronic GVHD at the Fred Hutchinson Cancer Research Center (FHCRC)/Seattle Cancer Care Alliance (SCCA) demonstrated that although 51% patients were able to stop IST at least one time, 46% of these patients required resumption of IST after a median of 3.4 months off therapy (IQR 2.1-8.0), due to GVHD exacerbation (9). Among patients stopping IST a second time, 30% restarted at a median of 6 months.

Resumption of IST for chronic GVHD exacerbation may increase the morbidity and mortality of patients, since common practice is to reinstitute high doses of IST initially, followed by a taper again to the lowest dose. Additionally, GVHD may fail to be controlled after resumption of IST, or irreversible organ damage may occur each time GVHD symptoms flare.

A potential alternative approach to the current practice of repeated attempts to taper and stop IST is continuation of IST.

The purpose of this study is to enroll a cohort of patients with chronic GVHD whose their treating physician is planning to taper their IST to off, and to randomize them to either discontinuation of IST (standard approach) or continuation of IST for another 9 months (investigational approach), in order to evaluate the effect of prolonged IST on chronic GVHD control, with the hypothesis that this approach would decrease the risk of GVHD exacerbation and decrease the need to resume high doses of IST. The rational for the 9 months extended IST in the continuation IST arm is retrospective data demonstrating

that >75% of patients who resumed IST after discontinuation, restarted within 9 months of IST discontinuation.

The rationale for the feasibility study is that a large sample size is needed to demonstrate statistically significant differences between the two treatment approaches. Thus, prior to proceeding with a large study we need to conduct a feasibility study to evaluate whether patients can be enrolled, randomized, and follow their assigned treatment, and to assess whether the observations about IST resumption in the retrospective study appear accurate. We acknowledge the heterogeneity among the target patient population (e.g. donor and stem cell source, time since transplant, and IST), but despite this heterogeneity when patients are ready to taper IST they are more similar than different in their clinical status. Information from this feasibility study are necessary to help us design a larger study and apply for external funding. In the larger study, we plan to use stratified randomization to help balance underlying patient and transplant characteristics.

Biological samples will be collected during the study to analysis of blood profiles and cellular signatures of “functional” tolerance and biomarkers of GVHD exacerbation.

2. Objectives

2.1 Primary Objective

Assess feasibility of enrolling and randomizing patients with chronic GVHD to discontinuation (standard of care) versus continuation (investigation) of IST.

2.2 Secondary Objectives

- Assess feasibility of enrolling and randomizing patients who are not local, and evaluate the quality of data received for those patients.
- Assess whether prolonged IST decreases the need for pulses of high dose IST.
- Evaluate the effect of prolonged IST on chronic GVHD manifestations and severity, risk of relapse, infection and organ toxicity.

3. Endpoints

3.1 Primary Endpoint

- Number of patients enrolled on the study (signed consent) in 2 years

3.2 Secondary Endpoint

- Successful randomization of patients
- Compliance with treatment and data collection as outlined in the protocol
- Evaluate enrollment rate and quality of data of patients who are not local
- Rate of IST resumption (discontinuation IST arm)/increase IST dose (continuation IST arm) by 12 months after randomization

- New chronic GVHD manifestations and/or worsening of existing manifestations, recurrent malignancy by 12 months after randomization, grade ≥ 3 infections, and grade ≥ 3 organ toxicity.

4. Stopping Rules

1. Accrual of less than 12 patients in the first year

5. Subject Selection

5.1 Inclusion criteria

1. Prior first allogeneic stem cell transplant, with any graft source, donor type, and GVHD prophylaxis.
2. Patients who are on one systemic immunosuppressive agent for chronic GVHD with a plan to withdraw all systemic IST. Hydrocortisone or prednisone continued for treatment of adrenal insufficiency are not considered a systemic IST.
3. No evidence of malignancy at the time of enrollment.
4. Agree to be evaluated at the transplant center or by local provider every 3 months for 12 months after randomization.
5. Agreement to be contacted by phone or e-mail for health status evaluation for up to 3 years.
6. Signed, informed consent

5.2 Exclusion criteria

1. Inability to comply with study procedures
2. Pregnancy

6. Study Procedures

6.1 Study Design

We plan to enroll 40 patients in 2 years. Patients are eligible for enrollment at any time after an allogeneic transplant, as long as they were diagnosed with chronic GVHD, are on one immunosuppression agent, and are planning to withdraw all IST. Patients will be randomized to either IST discontinuation (following standard of care practice) or continuation of IST for an additional 9 months (investigational). If patients are enrolled on the study prior to reaching the IST dose that the attending physician recommends

they continue should they be randomized to the continuation IST arm, randomization will take place before the patient gets to the IST dose that would be continued if they are randomized to the IST continuation arm (investigational arm). If patients are enrolled on the study while they are already taking the IST dose that the attending physician recommends they continue should they be randomized to the continuation IST arm, randomization will take place at time of enrollment (Figure 1). Randomization will occur within three months of study enrollment. Patients will be actively followed for 12 months after randomization. After active participation will continue long term annual follow up via chart review.

Patients on the discontinuation IST arm will have their IST tapered and discontinued per the plan of the treating physician, while patients on the continuation IST arm will continue a fixed dose IST for an additional 9 months with no taper. After 9 months, IST may be tapered.

The dose of IST to be continued, if a patient is randomized to the continuation IST arm, will be determined by the attending physician at the time of enrollment based on the following overarching guidelines in the table below:

Immunosuppressive therapy	**Age 18 years**	**Age <18 years**
Cyclosporine	Continuation dose should result in a level < 120 ng/mL	
Tacrolimus	Continuation dose should result in a level < 5 ng/mL	
Sirolimus	Continuation dose should result in a level < 3 ng/mL	
Mycophenolate mofetil	Continuation dose ≤ 500 mg BID	Continuation dose ≤ 7.5 mg/kg BID
Prednisone	< 20 mg/day **or** < 40 mg every other day	< 0.25 mg/kg/day **or** < 0.5 mg every other day
Any other agent	Defined by the treating physician at the time of enrollment	

For further evaluation of adult patients' health status, adult participants will be asked to complete a survey (Appendix A) based on the PROMIS-29 and Lee Symptom Scale. Please note that patient surveys might be reformatted for ease of completion and to ensure uniform font and style in the two documents or to correct any formatting or typographical errors. However, no questions will be added without IRB approval.

Patients will be asked to complete the survey at enrollment, randomization, every 3 months after randomization, at the end of the active study participation (12 months after randomization), and if IST resumed/dose increased (if still during the active study participation period).

The Patient-Reported Outcomes Measurement Information System (PROMIS®), is a set of person-centered measures developed with NCI support (10). The PROMIS-29 profile contains 7 PROMIS domains with 4 questions each (short-forms using Likert scales), and one pain intensity (0-10) question. All PROMIS scores use a standardized t-score metric against normative data for the U.S. general population (11, 12). The scale takes less than 5 minutes to complete.

The Lee cGVHD symptom scale is a 30 item measure with 7 domains capturing bothersome symptoms from chronic GVHD (13). The Lee cGVHD symptom scale is sensitive to change in patient status with 6-7 point differences being clinically meaningful (14, 15). The scale takes 2-5 minutes to complete.

Pediatric patients will not be asked to complete the surveys, which were designed to the adult population. No Patient-Reported Outcomes Measurement or symptom scale surveys have been validated for transplant pediatric population. Thus, pediatric participants would not be asked to complete surveys.

Whole blood samples will be collected for research. All effort will be made to collect 40 mL blood samples (see table for children ≤40 kg) at enrollment, randomization, and monthly until one year after randomization, and at times of IST resumption or dose increase.

	25-40 kg	10-24.99 kg	<10 kg
Maximum volume of each blood draw	20 mL	10 mL	5 mL
Maximum volume in 1 year	260 mL	130 mL	65 mL

Patients may participate without donating blood but every effort will be made to collect the samples, including use of remote draw and overnight shipping.

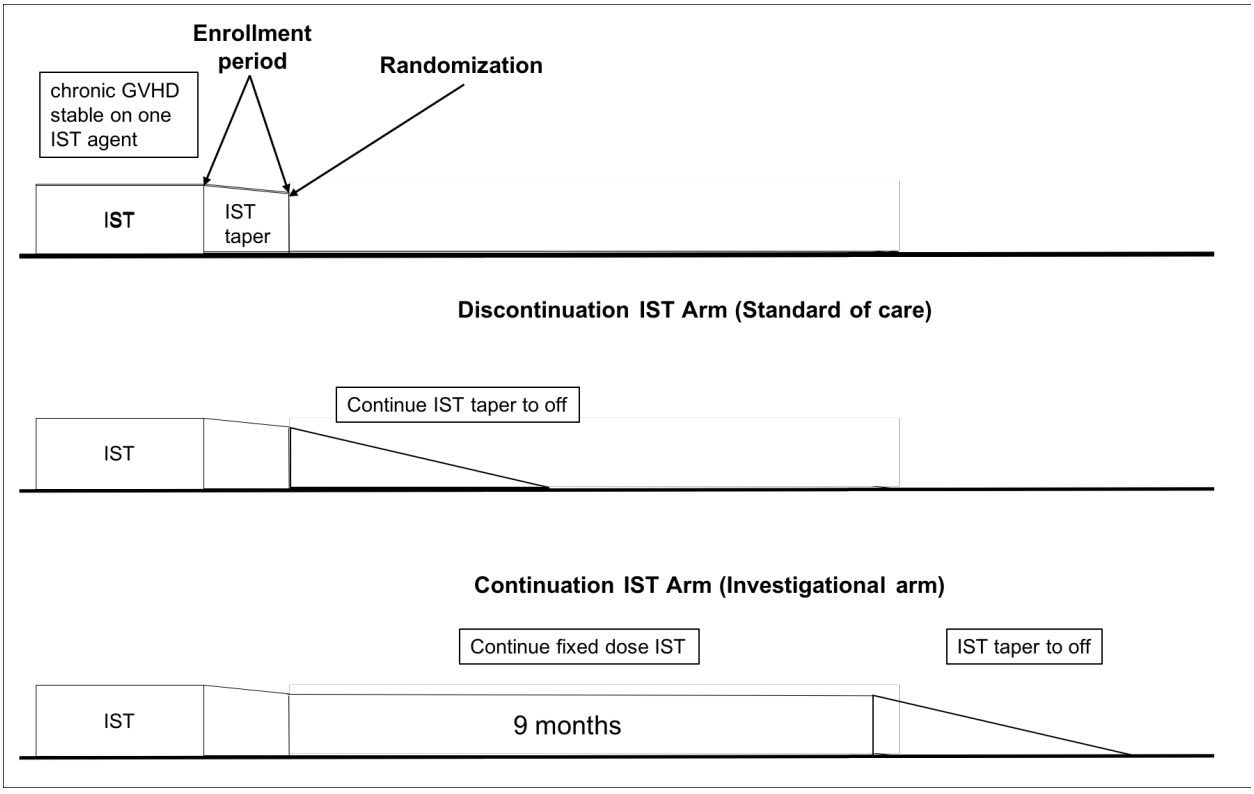

Figure 1. Study design

6.2 Study Design Rationale

Need for a feasibility study: This study is based on the hypothesis that prolonged low dose IST will prevent GVHD exacerbation and need to resume of high doses of IST. Preliminary data in support of this hypothesis are derived from a retrospective study demonstrating that approximately half of patients with chronic GVHD who stop IST need to restart treatment after a median of 3-6 months. The only way to test this hypothesis is with a randomized trial but the sample size for such a study is prohibitive without evidence that patients can be enrolled and randomized, that they will follow their assigned treatment, and that the observations about IST resumption in the retrospective study appear accurate.

Justification for allowing heterogeneity in last agent, tapering schedules, and dose to continue in the intervention arm: As patients with chronic GVHD respond to a variety of immunosuppressive agents and doses, there is no unified treatment protocol for chronic GVHD. Similarly there are no uniform criteria when attempts to stop IST should be initiated. In our retrospective study the last immunosuppressive regimen to be discontinued was variable, including calcineurin inhibitors (43%), prednisone (28%), sirolimus (19%), or mycophenolate mofetil (10%). Thus, after discussion with the LTFU attendings, we elected to allow heterogeneity in plans for IST taper timing and speed. This study design mirrors routine clinical practice and allows us to capture data about the most common practices regarding IST discontinuation. At the time of enrollment, physicians must specify the dose/schedule at which they are comfortable randomizing a patient to possibly continue stable treatment for an additional 9 months. Ideally, this would be a dose that does not cause toxicity and also controls GVHD.

Enrollment time: We will enroll patients at the time when they are only taking one immunosuppressive agent, chronic GVHD is under control and the plan is to start tapering IST, or when patients are already tapering IST. Patients may be enrolled on the study before or at the time they are taking the IST dose that the attending physician recommends they continue should they be randomized to the continuation IST arm. Enrolling patients before or at the time they reach the IST dose that may be continued should they be randomized to the continuation IST arm (Figure 1) allows us to present the protocol to patients when they are seen in the clinic, which will increase the chance of enrolling patients on the study (Patients with well controlled GVHD are seen in clinic infrequently and thus may be seen before or at the time they have already reached the lower IST dose to be continued).

6.3 Subject Registration and Informed Consent

Eligible subjects will be identified by the SCCA LTFU or SCH providers and the study staff. A complete, signed, study informed consent is required for registration.

Before enrollment, the study investigator or sub-investigators will discuss the study and consent form thoroughly with the potential participant. The study will be presented as objectively as possible and the potential risks and hazards of the study explained to the

subject. Consent will be obtained using forms approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center (FHCRC).

The study and consent form will be discussed with potential participants at their LTFU at the SCCA or SCH visits. However, if the patient requests to think about the study prior to making final decision, the study PI or sub-PI will call the patient about a week after his/her appointment, will review the study and consent form again, answer any questions the patient might have, and if the patient is interested he/she will sign consent over the phone. The rational for the telephone follow-up and not in person follow-up is that many of the patients are not local, and the phone follow-up will decrease burden on the patient. If patient would like to have in person follow-up this option would be available.

If subject signs the informed consent at home (after discussing the study procedure and its potential risk with the study investigator or sub-investigator), he/she will mail the signed informed consent form (ICF) to the FHCRC and the document will be signed by the person who obtained the consent over the phone. The investigator/sub-investigator will document the consent discussion in the medical record. A copy of the ICF will be provided to the subject. Signed ICFs will remain in each subject's chart.

6.4 Data Collection

Provider and patient assessments will be collected in the form of study surveys at enrollment, and if possible at randomization, and every three months for 12 months and at times of IST resumption or increased dose, if still during the period of active study participation. If patients cannot be seen at the SCCA or SCH clinic at these time points, an effort will be made to collect the pertinent information from the patients' local providers. The study team will contact participants monthly via phone or email to check on each patient's status. Additional information (e.g. laboratory test results) would be obtained from the patients' records.

For further evaluation of patients' health status, adult participants will be asked to complete a survey based on the PROMIS-29 and Lee symptoms scale (Appendix A). Patients will be asked to complete the survey at enrollment, randomization, every 3 months after randomization, at the end of the active study participation (12 months after randomization) and if IST resumed/dose increased (if still during the active study participation period). If a patient is not seen in clinic, questionnaires will be mailed to the patient.

Following the 12 months active participation period, participants will be followed by chart review annually to determine disease status, GVHD status, IST status, and survival.

6.5 Study Procedures

Eligible patients will be identified at Seattle Cancer Care Alliance or Seattle Children's Hospital by clinicians. Signed informed consent will be obtained by clinicians. All

females of childbearing potential will have a pregnancy test at enrollment. Pregnant women will be excluded from the study.

After consent, the clinician will complete the provider survey, the patient will complete the patient self-assessment survey, and an effort will be made to have a research blood sample drawn.

If patients are enrolled on the study prior to reaching the IST dose the attending physician recommends they continue should they be randomized to the continuation IST arm, then randomization will take place before the patient gets to the IST dose that would be continued if they are randomized to the IST continuation arm (investigational arm). If patients are enrolled on the study while they are already taking the IST dose that the attending physician recommends they continue should they be randomized to the continuation IST arm, randomization will take place at time of enrollment (Figure 1).

The clinician and the patient will be informed about the randomization, and further IST management would be according to the study arm the patient was randomized to, as described above.

There is no financial compensation to patients for participating in this study.

Participants will be contacted by the study coordinator via phone or email (according to their preference) monthly, if they are not seen at the LTFU clinic. The study coordinator will review health status, confirm future clinic schedules and check whether IST was restarted for GVHD. Following the 12 months active participation period, participants will be followed by chart review annually to determine disease status, GVHD status, IST status, and survival.

Research blood samples will be collected from patients at time of enrollment, and potentially several time points after enrollment as discussed above in section 6.1.

Data will be entered electronically into a password-protected database using only the participant study ID. All data will be maintained in secured areas (locked file cabinets and password-protected electronic databases).

If a patient relapses with their primary disease and requires systemic anti-cancer treatment, data collection from the patient and clinician will cease and no additional research samples will be taken. The patient will continue to be followed via chart review.

The intent is to randomize patients within three months of enrollment. If a patient has not been randomized within three months of enrollment, data collection from the patient and clinician will cease and no additional research samples will be taken. The patient will continue to be followed via chart review.

If a participant or the partner of a research participant becomes pregnant during the study, the principal investigator will follow the pregnant female for pregnancy outcome.

6.6 Adverse Reactions and their Management

Prolonged IST on the continuation IST arm may result in increased risk of infection, treatment related organ toxicity, and increased risk for relapse. Earlier discontinuation of IST on the discontinuation arm may result in increased risk for GVHD exacerbation, required initiation of high dose immunosuppression, which again may result in increased risk of infection, treatment related organ toxicity, and increased risk for relapse. Treatment of any complication will be at the discretion of the patient's provider.

Blood collection for research purposes will usually be done at the same time as clinical sampling.

If an adverse event occurs as a result of study participation, the PI will ensure appropriate follow-up is carried out until the effects of the adverse event are resolved. If the study staff becomes aware of any unanticipated severe adverse reactions due to study participation, the circumstances will be reported to the IRB. To note, clinical events and/or laboratory findings related to IST will not be reported as adverse events, since both discontinuation or prolonged continuation of IST are used in practice.

6.7 Data and Specimen Storage

Blood samples will be collected for future laboratory studies. Participants will donate whole blood at enrollment and additional time points as detailed in section 6.1. Samples will be processed according to standard procedures and labeled with a sample identification number. Samples will be stored in a repository and may be used to study chronic GVHD and/or other transplant complications.

All study data will be stored in the master database using only the participant's unique identifier. The link to the participant's identity will be maintained separately from the study data.

7. Statistical Considerations

7.1. Statistical Analysis Plan

7.1.1. Primary Endpoint

The primary objective of this study is to assess feasibility of enrolling and randomizing patients with chronic GVHD to discontinuation (discontinuation IST arm; standard of care) versus prolonged continuation of IST (continuation IST arm; investigational arm).

Feasibility will be assessed by accrual rate of 20 patients per year. Early stopping of the accrual to the study is low accrual rate defined as less than 12 patients enrolled in the first year.

7.1.2. Secondary Endpoints

The secondary objective of this study includes three parts: 1) treatment compliance including rate of patient reaching randomization and rate of patients following study specific IST management based on study arm; 2) assess feasibility (enrollment and data collection) for patients who are not local; and 3) assess whether continuation IST decreases the need for pulses of high does IST and efficacy and safety evaluation of continuation IST arm

Secondary endpoint analyses will be descriptive. The analyses will be conducted by overall population, patients who are not local, and by arm, as applicable.

The summary statistics for continuous variables will include sample size, mean, standard deviation (SD), median, minimum and maximum for both baseline and post-baseline measurements (if applicable). The summary statistics for categorical variables will include sample size, frequency and percentages. The difference between two arms will be examined if applicable. Fisher's exact test will be proposed to test the difference between two arms for categorical variables.

7.1.3. Methods

Descriptive summary table will be provided for overall study population, and by each arm, respectively. The summary statistics for continuous variables will include sample size, mean, standard deviation (SD), median, minimum and maximum for both baseline and post-baseline measurements (if applicable). The summary statistics for categorical variables will include sample size, frequency and percentages. The difference between the two arms will be examined if applicable. Fisher's exact test will be proposed to test the difference between two arms for categorical variables.

7.2. Sample Size and Power

This feasibility study is to assess the ability to enroll and randomize patients with chronic GVHD to discontinuation versus continuation of IST. Sample size of 40 patients is based on the anticipated availability of eligible patients. Although the study is not powered based on a specific null hypothesis, if 20 patients are enrolled in each arm, we will have 83% power to see statistically significant difference between two arms (at the two-sided level of 0.1) if the true 12 months rate of IST resumption in discontinuation IST arm is 75% and true 12 months rate of increase IST dose in investigation arm is 30%.

8. Risks and Discomforts

Prolonged IST on the continuation IST arm (investigational arm) may result in increased risk of infection, treatment related organ toxicity, and increased risk for relapse. Earlier discontinuation of IST on the discontinuation arm (standard of care) may result in increased risk for GVHD exacerbation, required initiation of high dose immunosuppression, which again may result in increased risk of infection, treatment

related organ toxicity, and increased risk for relapse. Treatment of any complication will be at the discretion of the patient's provider.

Blood collection for research purposes will usually be done at the same time as clinical sampling.

9. Potential Benefits

Based on retrospective data demonstrating that approximately 50% of patients who stop IST require resumption of IST due to GVHD exacerbation, the continuation arm of this study (investigational arm) offers potential benefit of decreasing the risk of chronic GVHD exacerbation and decreasing the need for resuming high-dose IST.

10. Adverse Events/Serious Adverse Events

10.1 Adverse Events

According to ICH guidelines (Federal Register. 1997; 62(90):25691-25709) and 21 CFR 312.32, IND Safety Reports, and ICH E2A, Definitions and Standards for Expedited Reporting, an adverse event is defined as follows:

> *An adverse event is any untoward medical occurrence in a clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.*
>
> *Abnormal laboratory values for laboratory parameters specified in the study should not be recorded as an adverse event unless an intervention is required (repeat testing to confirm the abnormality is not considered intervention), the laboratory abnormality results in a serious adverse event or the adverse event results in study termination or interruption/discontinuation of study treatment.*
>
> *Medical conditions present at screening (i.e., before the study treatment is administered) are not adverse events and should not be recorded on adverse event pages of the CRFs. These medical conditions should be adequately documented on the subject chart. However, medical conditions present at baseline that worsen in intensity or frequency during the treatment or post-treatment periods should be reported and recorded as adverse events.*

Events that do not meet the definition of an AE or SAE include:

- Any clinically significant abnormal laboratory finding or other abnormal safety assessments that is associated with the underlying disease, unless

judged by the investigator to be more severe than expected for the subject's condition.

- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition
- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen
- Clinical events or laboratory findings related to immunosuppressive therapy

10.2 Serious Adverse Events

An adverse event should be classified as an SAE if it meets one of the following criteria:

Fatal	Adverse event results in death.
Life threatening:	The adverse events placed the subject at immediate risk of death. This classification did not apply to an adverse event that hypothetically might cause death if it were more severe.
Hospitalization:	It required or prolonged inpatient hospitalization. Hospitalizations for elective medical or surgical procedures or treatments planned before enrollment in the treatment plan or routine check-ups are not SAEs by this criterion. Admission to a palliative unit or hospice care facility is not considered to be a hospitalization.
Disabling/incapacitating	Resulted in a substantial and permanent disruption of the subject's ability to carry out normal life functions.
Congenital anomaly or birth defect:	An adverse outcome in a child or fetus of a subject exposed to the molecule or treatment plan regimen before conception or during pregnancy.
Medically significant:	The adverse event did not meet any of the above criteria, but could have jeopardized the subject and might have required medical or surgical intervention to prevent one of the outcomes listed above.

10.3 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

An event which is part of the natural course of the disease under study (i.e., disease progression) does not need to be reported as an SAE. However, if the progression of the underlying disease is greater than that which would normally be expected for the subject, or if the investigator considers that there was a causal relationship between treatment with investigational product or protocol design/procedures and the disease progression, then this must be reported as an SAE.

10.4 Unexpected Adverse Event

An unexpected adverse event is defined as an event that has a nature or severity, or frequency that is not consistent with the applicable investigator brochure, or the prior medical condition of the subject or other treatment given to the subject. “Unexpected,” as used in this definition, refers to an adverse drug experience that has not been previously observed and reported in preclinical or clinical studies rather than an experience that has not been anticipated based on the pharmacological properties of the study drug.

10.5 Monitoring and Recording Adverse Events

All AEs will be assessed by the investigator or qualified designee and recorded in the CRFs. The investigator should attempt to establish a diagnosis of the event on the basis of signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the adverse event and/or serious adverse event and not described as the individual signs or symptoms. The following information should be recorded:

- Description of the adverse event using concise medical terminology
- Description as to whether or not the adverse event is serious, noting all criteria that apply
- The start date (date of adverse event onset)
- The stop date (date of adverse event resolution)
- The severity (grade) of the adverse event
- A description of the potential relatedness of the adverse event to study drug, a study procedure, or other causality
- The action taken due to the adverse event
- The outcome of the adverse event

If an adverse event occurs as a result of study participation, the PI will ensure appropriate follow-up is carried out until the effects of the adverse event are resolved. If the study staff becomes aware of any unanticipated severe adverse reactions due to study participation, the circumstances will be immediately reported to the IRB. To note, clinical events related to IST will not be reported as adverse events, since both discontinuation or prolonged continuation of IST are used in practice. All AEs and SAEs will be reported to the DSMC at least annually.

10.6 Grading Adverse Event Severity

All AEs will be graded in severity according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. If a CTCAE criterion does not exist, the investigator should use the grade or adjectives: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), or Grade 5 (fatal) to describe the maximum intensity of the adverse event.

10.7 Attribution of an Adverse Event

Association or relatedness to the study agent will be assessed by the investigator as follows:

- **Definite**: The event follows a reasonable temporal sequence from exposure to the investigational agent, has been previously described in association with the investigational agent, and cannot reasonably be attributed to other factors such as the subject's clinical state, other therapeutic interventions or concomitant medications; AND the event disappears or improves with withdrawal of the investigational agent and/or re-appears on re-exposure (e.g., in the event of an infusion reaction).
- **Probable**: The event follows a reasonable temporal sequence from exposure to the investigational agent and has been previously been described in association with the investigational agent OR cannot reasonably be attributed to other factors such as the subject's clinical state, other therapeutic interventions or concomitant medications.
- **Possible**: The event follows a reasonable temporal sequence from exposure to the investigational agent, but could be attributable to other factors such as the subject's clinical state, other therapeutic interventions or concomitant medications.
- **Unlikely**: Toxicity is doubtfully related to the investigational agent(s). The event may be attributable to other factors such as the subject's clinical state, other therapeutic interventions or concomitant medications.
- **Unrelated**: The event is clearly related to other factors such as the subject's clinical state, other therapeutic interventions or concomitant medications.

For general AE assessment, an AE is considered related if it is assessed as definitely, probably, or possibly related; unrelated if it is assessed as unlikely related or unrelated.

10.8 Adverse Event Recording Period

AEs will be monitored and recorded in study-specific case report forms (CRFs) from the time of consent through the end of active follow-up (~12 months after randomization).

11. Data and Safety Monitoring Plan

Institutional support of trial monitoring will be in accordance with the FHCRC/University of Washington Cancer Consortium Institutional Data and Safety Monitoring Plan. Under the provisions of this plan, FHCRC Clinical Research Support (CRS) coordinates data and compliance monitoring conducted by consultants, contract research organizations, or FHCRC employees unaffiliated with the conduct of the study. Independent monitoring visits occur at specified intervals determined by the assessed risk level of the study and the findings of previous visits per the institutional DSMP.

In addition, protocols are reviewed at least annually and as needed by the Consortium Data and Safety Monitoring Committee (DSMC), FHCRC Scientific Review Committee (SRC) and the FHCRC/University of Washington Cancer Consortium Institutional Review Board (IRB). The review committees evaluate accrual, adverse events, stopping rules, and adherence to the applicable data and safety monitoring plan for studies actively enrolling or treating subjects. The IRB reviews the study progress and safety information to assess continued acceptability of the risk-benefit ratio for human subjects. Approval of committees as applicable is necessary to continue the study.

The trial will comply with the standard guidelines set forth by these regulatory committees and other institutional, state and federal guidelines.

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11. Appendix

Appendix A. Patient Survey

Discontinuation versus continuation of immunosuppressive therapy (IST) in chronic Graft Versus Host Disease (GVHD)

Patient Survey

INSTRUCTIONS

This survey will provide us with important information about your health.

All your answers will be kept strictly confidential and will not be included in your medical record. The information that you provide will be combined with that of many other transplant patients before analysis.

Please read each question carefully. Circle or check off the answer that best describes how you feel.

While we ask that you answer each question, you are free to *not* answer any question that makes you feel uncomfortable. If none of the answers provided seems exactly right, choose the one that comes closest to being right for you. Some of the questions may seem the same. However, it is important that we ask about certain aspects of your health in different ways in order to fully understand how you are feeling.

When you have completed this survey, please give it back to the study coordinator or mail it back to us using the enclosed self-addressed, stamped envelope.

We greatly appreciate your participation.

Your name: _____ Date: _____

Appendix A. Patient Survey (cont.)

Section 1: Your Chronic Graft vs. Host Disease (GVHD) Symptoms

By circling one (1) number per line, please indicate how much you have been bothered by the following problems in the past 7 days:

SKIN:		Not at all	Slightly	Moderately	Quite a bit	Extremely
1.	Abnormal skin color……	0	1	2	3	4
2.	Rashes……	0	1	2	3	4
3.	Thickened skin……..……..	0	1	2	3	4
4.	Sores on skin……	0	1	2	3	4
5.	Itchy skin……..……	0	1	2	3	4
EYES AND MOUTH:		**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
6.	Dry eyes……	0	1	2	3	4
7.	Need to use eye drops frequently..	0	1	2	3	4
8.	Difficulty seeing clearly……	0	1	2	3	4
9.	Need to avoid certain foods due to mouth pain……	0	1	2	3	4
10.	Ulcers in mouth……	0	1	2	3	4
11.	Receiving nutrition from an intravenous line or feeding tube….	0	1	2	3	4
BREATHING:		**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
12.	Frequent cough……	0	1	2	3	4
13.	Colored sputum……	0	1	2	3	4
14.	Shortness of breath with exercise..	0	1	2	3	4
15.	Shortness of breath at rest……..	0	1	2	3	4
16.	Need to use oxygen……..	0	1	2	3	4

Appendix A. Patient Survey (cont.)

9962: Functional Tolerance after Allo HCT

EATING AND DIGESTION:	Not at all	Slightly	Moderately	Quite a bit	Extremely
17. Difficulty swallowing solid foods….	0	1	2	3	4
18. Difficulty swallowing liquids……	0	1	2	3	4
19. Vomiting……	0	1	2	3	4
20. Weight loss……	0	1	2	3	4
MUSCLES AND JOINTS:	**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
21. Joint and muscle aches……..	0	1	2	3	4
22. Limited joint movement……	0	1	2	3	4
23. Muscle cramps……..	0	1	2	3	4
24. Weak muscles……..	0	1	2	3	4
ENERGY:	**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
25. Loss of energy……	0	1	2	3	4
26. Need to sleep more/take naps…..	0	1	2	3	4
27. Fevers……	0	1	2	3	4
MENTAL AND EMOTIONAL:	**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
28. Depression……	0	1	2	3	4
29. Anxiety……..	0	1	2	3	4
30. Difficulty sleeping……	0	1	2	3	4

Appendix A. Patient Survey (cont.)

Section 2: PROMIS–29 Profile v2.0

Please respond to each question or statement by marking one box per row.

Physical Function	***Without any difficulty***	***With a little difficulty***	***With some difficulty***	***With much difficulty***	***Unable to do***
Are you able to do chores such as vacuuming or yard work?.....	☐	☐	☐	☐	☐
Are you able to go up and down stairs at a normal pace?.....	☐	☐	☐	☐	☐
Are you able to go for a walk of at least 15 minutes?.....	☐	☐	☐	☐	☐
Are you able to run errands and shop?.....	☐	☐	☐	☐	☐

Anxiety ***In the past 7 days…***	***Never***	***Rarely***	***Sometimes***	***Often***	***Always***
I felt fearful.....	☐	☐	☐	☐	☐
I found it hard to focus on anything other than my anxiety.....	☐	☐	☐	☐	☐
My worries overwhelmed me...	☐	☐	☐	☐	☐
I felt uneasy.....	☐	☐	☐	☐	☐

Depression ***In the past 7 days...***	***Never***	***Rarely***	***Sometimes***	***Often***	***Always***
I felt worthless	☐	☐	☐	☐	☐
I felt helpless.....	☐	☐	☐	☐	☐
I felt depressed.....	☐	☐	☐	☐	☐
I felt hopeless.....	☐	☐	☐	☐	☐

Fatigue ***During the past 7 days…***	***Not at all***	***A little bit***	***Somewhat***	***Quite a bit***	***Very much***
I feel fatigued	☐	☐	☐	☐	☐
I have trouble starting things because I am tired.....	☐	☐	☐	☐	☐

Appendix A. Patient Survey (cont.)

Fatigue ***During the past 7 days…***	***Not at all***	***A little bit***	***Somewhat***	***Quite a bit***	***Very much***
How run-down did you feel on average?.....	☐	☐	☐	☐	☐
How fatigued were you on average?	☐	☐	☐	☐	☐

Sleep Disturbance ***In the past 7 days…***	***Very poor***	***Poor***	***Fair***	***Good***	***Very good***
My sleep quality was.....	☐	☐	☐	☐	☐
In the past 7 days…	***Not at all***	***A little bit***	***Somewhat***	***Quite a bit***	***Very much***
My sleep was refreshing.....	☐	☐	☐	☐	☐
I had a problem with my sleep	☐	☐	☐	☐	☐
I had difficulty falling asleep....	☐	☐	☐	☐	☐

Ability to Participate in Social Roles and Activities					
	Never	***Rarely***	***Sometimes***	***Usually***	***Always***
I have trouble doing all of my regular leisure activities with others.....	☐	☐	☐	☐	☐
I have trouble doing all of the family activities that I want to do.....	☐	☐	☐	☐	☐
I have trouble doing all of my usual work (include work at home)	☐	☐	☐	☐	☐
I have trouble doing all of the activities with friends that I want to do	☐	☐	☐	☐	☐

Pain Interference ***In the past 7 days…***	***Not at all***	***A little bit***	***Somewhat***	***Quite a bit***	***Very much***
How much did pain interfere with your day to day activities?	☐	☐	☐	☐	☐
How much did pain interfere with work around the home?	☐	☐	☐	☐	☐
How much did pain interfere with your ability to participate in social activities?.....	☐	☐	☐	☐	☐
How much did pain interfere with your household chores?	☐	☐	☐	☐	☐

Appendix A. Patient Survey (cont.)

Pain Intensity

In the past 7 days…

How would you rate your pain on average?.....	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
	No pain										**Worst imaginable pain**

For office use only:

Study ID	*Initials (First, Last)*	*Date completed:*	*Date received:*
Timepoint: ☐ *Enrollment* ☐ *Randomization* ☐ *Month 3* ☐ *Month 6* ☐ *Month 9* ☐ *Month 12* ☐ *IST change*		*Date entered:*	*v1.1*