Haploidentical Stem Cell Transplant using Post Transplant Cyclophosphamide for GvHD Prophylaxis: A Pilot Study
Comprehensive Cancer Center of Wake Forest University
CCCWFU # 97214
ClinicalTrials.gov; NCT02248597

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**Confidential**

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# 1.0 Introduction and Background

Hematopoietic stem cell transplantation (HSCT) offers a curative potential for many hematological diseases including malignant, nonmalignant, and autoimmune disorders. However, the potential benefit of HSCT is directly offset by the risk of severe graft-versus-host disease (GvHD), which may lead to significant transplant associated morbidity and mortality. The risk of GvHD is directly proportional to the degree of HLA-disparity between the donor and recipient. For this reason, HLA-matched sibling transplants are associated with optimal outcomes.

Only 25% of patients have an HLA-identical sibling[1]. As a result, the majority of patients require an alternative donor source, usually from an unrelated adult donor. For more than 20 years the National Marrow Donor Program (NMDP) has been recruiting volunteer donors for patients without HLA identical siblings. However, many patients, especially patients from ethnic minority backgrounds, frequently lack a full matched donor. Due to the fact that there are only 600,000 registered African American adult donors compared to the 8 million white registered donors, African Americans are less likely to find HLA-matched unrelated donors[2]. By current estimates, approximately 6% of African Americans have an HLA-matched donor by high resolution available in the registry[3].

Haploidentical HSCT is an alternative for patients who do not have a fully HLA-matched donor. Almost all patients have an available HLA-haploidentical donor, which may include a parent, sibling, or child. However, early attempts at performing T cell–replete haploidentical transplantations using conventional preparative regimens have been associated with very high rates of graft-versus-host disease (GVHD) and graft rejection.[4] Ex-vivo T cell depletion of the graft in combination with intensive preparative regimens have been employed to improve haploidentical transplant outcomes, but have often been associated high rates of infectious complications and non-relapse mortality (NRM).[5,6] Recent work has demonstrated that the addition of high dose Cytoxan administered early post-transplant improves outcomes for patients receiving a haploidentical HSCT, and has been associated with acceptable rates of NRM and GVHD in single- and multi institution studies.[7-9] Most recently, outcomes after T cell–replete HLA-haploidentical HSCT using post-transplantation cyclophosphamide have been found to be equivalent to those of match-related donor (MRD) and matched unrelated donor (MUD) transplantations.[10]

We propose a pilot study of performing haploidentical HSCT at our institution using post-transplant cyclophosphamide to prevent GvHD and improve clinical outcomes. This protocol will be offered to subjects with hematologic malignancies who are eligible to receive a HSCT for curative intent with an available familial haploidentical (4 to 6 out of 8 HLA loci-matched) donor. A reduced intensity preparative regimen will be used in the protocol.

# 2.0 Objectives

## 2.1 Primary Objective

**2.1.1** To determine if haploidentical stem cell transplant using post-transplant cyclophosphamide results in 60% or better disease free survival (DFS) at 12 months at our institution.

## 2.2 Secondary Objective

**2.2.1** To determine the rate of acute and chronic GvHD, non-relapse mortality, and relapse.

# 3.0 Inclusion/Exclusion Criteria

## 3.1 Inclusion Criteria

3.1.1 Diagnosis of a hematological malignancy requiring an allogeneic stem cell transplant consistent with the standard of care.

3.1.2 Remission of any acute hematologic malignancy or adequate disease control for chronic malignancies.

3.1.3 Ages 18-69 years old.

3.1.4 Available familial haploidentical (4 to 6 out of 8 HLA loci-matched) donor.

## 3.2 Exclusion Criteria

3.2.1 Significant organ dysfunction defined as:
3.2.1.1 LV EF < 50% (evaluated by echocardiogram or MRI).

3.2.1.2 DLCO or FEV1 < 65% predicted

3.2.1.3 AST/ALT > 2.5 x ULN

3.2.1.4 Bilirubin > 1.5 x ULN

3.2.1.5 Serum Cr > 2mg/dL, dialysis, or prior renal transplant

3.2.2 HIV positive (Recipients who are positive for hepatitis B (HBV), hepatitis C (HCV) or human T-cell lymphotropic virus (HTLV-I/II) are not excluded from participation)

3.2.3 Positive pregnancy test for women of childbearing age.

3.2.4 Major anticipated illness or organ failure incompatible with survival form transplant.

3.2.5 Severe psychiatric illness or mental deficiency sufficiently severe as to make compliance with the transplant treatment unlikely and informed consent impossible.

### 3.3 Inclusion of Women and Minorities

Men and women of all races and ethnicities who meet the above-described inclusion and exclusion criteria are eligible to participate in this study.

### 3.4 Donor Selection Criteria

3.4.1 Avoid donor specific antibodies (DSA). Select donors with a negative anti-donor cross-match.

3.4.2 Donor with full haplotype HLA-mismatch will be preferred (4 out of 8 HLA match) to maximize GVL.

3.4.3 Male donors will be preferred to avoid reactivity against H-Y minor histocompatibility antigens and associated risk of risk of acute GvHD, especially grafts from multiparous women.

3.4.4 Younger donors will be preferred. Younger donor age has been associated with better patient survival in the MUD SCT setting.

3.4.5 NIMA, IPA, and NK reactivity will not be included in selection criteria due to lack of evidence for impact on clinical outcomes and clinical utility.

## 4.0 Registration Procedures

All patients entered on any CCCWFU trial, whether treatment, companion, or cancer control trial, **must** be registered with the CCCWFU Protocol Registrar or entered into ORIS Screening Log within 24 hours of Informed Consent. Patients **must** be registered prior to the initiation of treatment.

In order to ensure prompt registration of your patient, please:
1. Complete the Eligibility Checklist (Appendix A)
2. Complete the Protocol Registration Form (Appendix B)
3. Alert the CCCWFU registrar by phone, *and then* send the signed Informed Consent Form, Eligibility Checklist and Protocol Registration Form to the registrar, either by fax or e-mail.

<u>Contact Information:</u>

Protocol Registrar PHONE (336) 713-6767
Protocol Registrar FAX (336) 713-6772
Protocol Registrar E-MAIL (registra@wakehealth.edu)
*Protocol Registration is open from 8:30 AM - 4:00 PM, Monday-Friday.

4. Please fax/e-mail the eligibility checklist along with the completed registration form. Ensure that the source documents column of the checklist is complete and that the form is signed by either the research nurse or CRA. Patients **will not** be registered if forms are incomplete.

Note: If labs were performed at an outside institution, please provide a printout of the results. Please ensure that the most recent lab values are sent.

To complete the registration process, the Registrar will:

- assign a patient study number
- register the patient on the study

## 5.0 Study Procedures

| | Pre-Study[A] | On-Study | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Day -3 | Day -2 | Day 0 | Days 3 and 4 | Day 15[C] | Day 30[C] | Day 45[C] | Day 60[C] | Day 100[D] | 6 months post-transplant[D] | 12 months post-transplant[D] |
| Informed Consent | X | | | | | | | | | | | |
| Medical History | X | | | | | | | | | | | |
| Cyclophosphamide | | | | | X | | | | | | | |
| Stem cell transplant | | | | X | | | | | | | | |
| AE Collection[B] | X | X | X | X | X | X | X | X | X | X | | |
| Data Collection (Appendix E) | | | | | | X | X | X | X | X | X | X |
| | | | | | | | | | | | | |
| A: Pre-study requirements must be completed prior to registration<br>BAE collection of only grade 3+ adverse events<br>C: Visit window is +/- 4 days of listed Day post-transplant.<br>D. Visit window is +/- 14 days of listed Day post-transplant | | | | | | | | | | | | |

### 5.1 Participant Recruitment

The Bone Marrow Transplant Program at Wake Forest University Baptist Medical Center performs over 100 stem cell transplants a year, approximately one third of which are allogeneic. Patients will be recruited for this protocol after referral to Wake Forest University Baptist Medical Center, and if deemed eligible to receive an allogeneic stem cell transplant as standard of care treatment of their disease.

### 5.2 Transplant Preparative Regimen

A Reduced Intensity Conditioning (RIC) Regimen will be included in this study as follows:

a. Fludarabine 25 mg/m2/dose IV infusion over 30 minutes administered once daily for 3 doses on Days -5, -4, and -3 (total dose of 75 mg/m2)

b. Total body irradiation (TBI): **600 cGy** divided in 4 x 150 cGy fractions, twice daily over days -2, -1.

### 5.3 Stem Cell Transplant Day 0.

On the day of transplant, recipients will receive an infusion of the stem cell product with a target cell dose per recipient body weight of 3 - 5 x $10^6$ CD34+ cells/ kg.

### 5.4 Post-transplant GvHD Prophylaxis.

1. Cyclophosphamide 50 mg/kg IV will be administered once per day on days 3 and 4 after HSCT.
2. Tacrolimus PO from days 5 to 120 , with a target level of 4 to 8 ng/mL.
3. Cellcept 15 mg/kg PO rounded to the nearest 500 mg and may be adjusted for therapeutic levels as appropriate on days 5 to 35.

### 5.5 Infection Prophylaxis.

1. G-CSF 5 g/kg was administered from day +5 until neutrophil recovery.
2. PCP, antiviral, and antifungal standard of care prophylaxis will be administered to all patients after transplantation.

### 5.6 Concomitant Medications and Supportive Care

Supportive care will be administered as per the guidelines set forth in *Biol Blood Marrow Transplant* 2009;15(10):1143-1238.

5.6.1 High fevers and rigors commonly are associated with haploidentical immunotherapy. Immunosuppressive therapy given after transplant but prior to day + 5 may decrease the effect of post-transplant Cytoxan (PTCy) and increase the risk of GVHD. **Therefore, immunosuppressive therapy (i.e., steroids) needs to be avoided prior to day + 5 after SCT.** To treat fevers and rigors associated with immunotherapy, verify that neutropenic fever protocols are being followed. May also consider the following agents:

- Acetaminophen
- Antihistamines
- Demerol or morphine for rigors
- Ibuprofen (caution with low platelets. May need to be accompanied by platelet transfusions.)

5.6.2 BK-induced Hemorrhagic Cystitis may occur in most patients receiving BuFlu conditioning, and may be treated with:

- Supportive care for symptoms, i.e., pain relief
- Bladder irrigation
- Intravesicular cidofovir

### 5.7 Duration of Study Participation and Criteria for Removal from Study

Participants may remain on study until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient withdraws consent to participate
- General or specific changes in the patient's condition render the patient unacceptable for further participation in the judgment of the investigator

## 6.0 Adverse Event Monitoring and Reporting

### 6.1 Adverse Event List

Potential adverse events include infections, GvHD, toxicity to chemotherapy. For this study, we will capture all Grade 3+ adverse events. Those that can be attributed to Cytoxan by the PI or designee will be recorded in the study's database. Patients should be followed for Grade 3+ AEs up to 100 days post-transplant. After 100 days post-transplant, patients will continue to be monitored only for GvHD, Relapse, and/or Death.

### 6.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

- **'Expectedness'**: AEs can be 'Unexpected' or 'Expected' (see Section 7.1 above) for expedited reporting purposes only.

- **Attribution** of the AE:

  - Definite – The AE **is clearly related** to the study treatment.
  - Probable – The AE **is likely related** to the study treatment.
  - Possible – The AE **may be related** to the study treatment.
  - Unlikely – The AE **is doubtfully related** to the study treatment.
  - Unrelated – The AE **is clearly NOT related** to the study treatment.

### 6.3 STRC SAE Reporting Requirements

The Data Safety Monitoring Committee (DSMC) is responsible for reviewing SAEs for WFBCCC Institutional studies as outlined in Appendix B. All Adverse Events that occur during protocol intervention and are coded as either 1) unexpected grade 4, 2) unplanned inpatient hospitalization ≥ 24 hours (regardless of grade), or grade 5 (death) must be reported to the DSMC using the using the SAE console in WISER.

All WFBCCC Clinical Protocol and Data Management (CPDM) staff members assisting a Principal Investigator in investigating, documenting and reporting an SAE qualifying for DSMC reporting are responsible for informing a clinical member of the DSMC as well as the entire committee via the email notification procedure of the occurrence of an SAE.

### 6.4 WFUHS IRB AE Reporting Requirements

Any unanticipated problems involving risks to subjects or others and adverse events shall be promptly reported to the IRB, according to institutional policy. Reporting to the IRB is required regardless of the funding source, study sponsor, or whether the event involves an investigational or marketed drug, biologic or device. Reportable events are not limited to physical injury, but include psychological, economic and social harm. Reportable events may arise as a result of drugs, biological agents, devices, procedures or other interventions, or as a result of questionnaires, surveys, observations or other interactions with research subjects.

All members of the research team are responsible for the appropriate reporting to the IRB and other applicable parties of unanticipated problems involving risk to subjects or others. The Principal Investigator, however, is ultimately responsible for ensuring the prompt reporting of unanticipated problems involving risk to subjects or others to the IRB. The Principal Investigator is also responsible for ensuring that all reported unanticipated risks to subjects and others which they receive are reviewed to determine whether the report represents a change in the risks and/or benefits to study participants, and whether any changes in the informed consent, protocol or other study-related documents are required.

Any unanticipated problems involving risks to subjects or others occurring at a site where the study has been approved by the WFUHS IRB (internal events) must be reported to the WFUHS IRB within 7 calendar days of the investigator or other members of the study team becoming aware of the event.

Any unanticipated problems involving risks to subjects or others occurring at another site conducting the same study that has been approved by the WFUHS IRB (external events) must be reported to the WFUHS IRB within 7 calendar days of the investigator or other members of the study team becoming aware of the event.

Any event, incident, experience, or outcome that alters the risk versus potential benefit of the research and as a result warrants a substantive change in the research protocol or informed consent process/document in order to insure the safety, rights or welfare of research subjects.

## 7.0 Response Criteria

Relapse of disease after transplant will be determined by morphological, cytogenetic, and molecular testing specific for the hematological malignancy of the patient.

GvHD will be determined by the clinical criteria set forth in Appendix F and/or histological grading from biopsy.

Disease free survival will be defined as time from registration to death from any cause or relapse of disease.

Non-relapse mortality will be defined as time from registration to death due to anything other than r elapse of hematological malignancy. Patients who relapse will be treated as a competing risk.

Overall survival will be defined as time to death due to all causes.

## 8.0 Analytic Plan

Our primary objective is to determine if the twelve month disease free survival probability for patients treated with haploidentical stem cell transplant using post-transplant cyclophosphamide is 0.60. We will calculate the proportion of subjects alive with no relapse disease at 12 months and the corresponding 95% confidence interval using the normal approximation for binomial proportions. With 24 patients, we would need 16 or more patients for the lower bound of the 95% confidence interval to be above 0.60. If the lower bound of the confidence interval is above 0.6, we can be confident that the true proportion is also above 0.60. We will accrue up to two patients per month for one year. Once each participant has been in the study for one year, we will test our primary hypothesis. Patients will then be followed for an additional two years. We do not anticipate any drop outs.

We will monitor patients continuously throughout the study at regular clinic visits after transplant. If at any time six participants experience death or relapse within the first 12 months after transplant, the study will stop for futility.

To evaluate our primary objective, we will first consider twelve month disease free survival as a binary outcome. We will calculate the proportion of patients who experience death or disease relapse by one year and construct a corresponding 95% confidence interval using the normal approximation for binomial proportions. Additionally, we will treat disease free survival as a censored outcome. The survival function will be estimated and plotted using the method of Kaplan and Meier. Additionally, we will calculate the rates of acute and chronic GvHD, overall survival, and relapse (or death) in our study population at twelve months. To evaluate relapse-free mortality, we will estimate the cumulative incidence function in the presence of relapse.

## 9.0 Stopping Rules for Safety

We expect that the rate of non-relapse mortality (NRM) is 20% in this population. We have calculated the following stopping rules for safety that take into account this expected rate using a Bayesian design. The study will stop if the probability of the true NRM rate is greater than the anticipated rate (assumed 0.2) is more 0.90. We use a Beta distribution (alpha=1.0, beta= 1.5) as the prior distribution for the probability of non-relapse mortality, and we will start monitoring for safety when four deaths are observed.

| Number of patients | Stop if number of NRM by day-90 reaches or exceeds |
|---|---|
| ≤11 | 4 |
| ≤15 | 5 |
| ≤19 | 6 |

We conducted a simulation study to evaluate the performance of the above stopping rules using various probabilities of NRM. We first sampled 24 independent Bernoulli trials, each with a probability p of NRM.[11] Using the above stopping rules, we noted if the study would have stopped and how many NRM's were observed. We repeated this process 100,000 times. The results for several values of p are summarized in the table below.

| **Prob of NRM = p** | **10%** | **20%** | **30%** | **40%** | **50%** | **60%** | **70%** |
|---|---|---|---|---|---|---|---|
| Proportion of Stopped Studies | 2.40% | 26.43% | 66.28% | 91.47% | 98.93% | 99.93% | 99.99% |
| Average # of NRM | 2.70 | 4.79 | 7.20 | 9.60 | 12.00 | 14.40 | 16.80 |

If the true probability of NRM is very low (10%), the study is unlikely to stop for safety. Under our expected rate of NRM, the 26.43% of simulated studies stopped early for safety. When the true rate of NRM is more than twice than our expected rate, the study is very likely to stop. From the results of this simulation, we believe the stopping rules are appropriate.

## 10.0 Data Management

| Form | Database |
|---|---|
| Informed consent | WISER |
| Registration form | WISER |
| Data collection form | REDCap |

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# Appendix A – Eligibility Checklist

| **IRB Protocol No. IRB00029210** | **CCCWFU Protocol No. 97214** |
|---|---|
| **Study Title:** Haploidentical Stem Cell Transplant using Post Transplant Cyclophosphamide for GvHD Prophylaxis: A Pilot Study | |
| **Principal Investigator:** Dianna Howard, MD | |

| **Inclusion Criteria (as outlined in study protocol)** | **Criteria is met** | **Criteria is NOT met** | **Source Used to Confirm *** |
|---|---|---|---|
| Diagnosis of a hematological malignancy requiring an allogeneic stem cell transplant consistent with the standard of care. | ☐ | ☐ | |
| Remission of any acute hematologic malignancy or adequate disease control for chronic malignancies | ☐ | ☐ | |
| Ages 18-69 years old. | ☐ | ☐ | |
| Available familial haploidentical (4 to 6 out of 8 HLA loci-matched) donor. | ☐ | ☐ | |
| **Exclusion Criteria (as outlined in study protocol)** | **Criteria NOT present** | **Criteria is present** | **Source Used to Confirm *** |
| Significant organ dysfunction defined as: | | | |
| LV EF < 50% (evaluated by echocardiogram or MRI). | ☐ | ☐ | |
| DLCO or FEV1 < 65% predicted | ☐ | ☐ | |
| AST/ALT > 2.5 x ULN | ☐ | ☐ | |
| Bilirubin > 1.5 x ULN | ☐ | ☐ | |
| Serum Cr > 2mg/dL, dialysis, or prior renal transplant | ☐ | ☐ | |
| HIV positive (Recipients who are positive for hepatitis B (HBV), hepatitis C (HCV) or human T-cell lymphotropic virus (HTLV-I/II) are not excluded from participation) | ☐ | ☐ | |
| Positive pregnancy test for women of childbearing age. | ☐ | ☐ | |
| Major anticipated illness or organ failure incompatible with survival from transplant. | ☐ | ☐ | |
| Severe psychiatric illness or mental deficiency sufficiently severe as to make compliance with the transplant treatment unlikely and informed consent impossible. | ☐ | ☐ | |

This subject is ☐ eligible / ☐ ineligible for participation in this study.

ORIS Assigned PID: _____

Signature of research professional confirming eligibility:_____ Date: _____

Signature of Principal Investigator**: _____ Date: _____

* Examples of source documents include clinic note, pathology report, laboratory results, etc. When listing the source, please specifically state which document in the medical record was used to assess eligibility. Please also include the date on the document. Example: “Pathology report, 01/01/14” or “Clinic note, 01/01/14”

**Principal Investigator signature can be obtained following registration if needed

# Appendix B - Protocol Registration Form

**DEMOGRAPHICS**

Patient: Last Name: _____ First Name: _____

MRN: ___ ___ ___ ___ ___ ___ ___ ___ DOB (mm/dd/yy): __ __ / __ __ / __ __

SEX: ☐ Male ☐ Female

Ethnicity (choose one): ☐ Hispanic ☐Non-Hispanic

Race (choose all that apply):

☐ WHITE ☐BLACK ☐ ASIAN ☐ PACIFIC ISLANDER ☐ NATIVE AMERICAN

Height: ___ ___.___ inches Weight: ___ ___ ___.___lbs.(actual)

Surface Area: ___ ___.___$m^2$ Zip Code: ___ ___ ___ ___ ___

Primary Diagnosis: _____

Date of Diagnosis: ___ ___ /___ ___/___ ___

**PROTOCOL INFORMATION**

Date of Registration: ___ ___ / ___ ___ / ___ ___

MD Name (last) : _____

Date protocol treatment started: ___ ___ / ___ ___ / ___ ___

Informed written consent (consent must be signed prior to registration):

☐ YES ☐ NO

Date Consent Signed: ___ ___ / ___ ___ / ___ ___

PID # (to be assigned by ORIS): ___ ___ ___ ___ ___ ___ ___ ___

*Protocol Registrar can be contact by calling 336-713-6767 between 8:30 AM and 4:00 PM, Monday – Friday. Completed Eligibility Checklist and Protocol Registration Form must be hand delivered, faxed or e-mailed to the registrar at 336-7136772 or registra@wakehealth.edu.*

# Appendix C – Mandatory STRC SAE Reporting Requirements

| | |
|---|---|
| **Data and Safety Monitoring Committee (DSMC) Serious Adverse Event (SAE) Notification SOP** | **Date: 02/11/2021** |

**Mandatory DSMC SAE Reporting Requirements in WISER**

This document describes reporting requirements of adverse events from **WFBCCC Investigator Initiated interventional trials to the Data and Safety Monitoring Committee (DSMC).** A trial is considered a **WFBCCC Investigator Initiated interventional trial** if the following criteria are met:

1) The Principal Investigator (PI) of the trial is a member of a department at the Wake Forest University Baptist Medical Center.
2) WFBCCC is considered as the primary contributor to the design, implementation and/or monitoring of the trial.
3) The trial is designated as "Interventional" using the Clinical Research Categories definitions provided by the NCI in the Data Table 4 documentation. (https://cancercenters.cancer.gov/GrantsFunding/DataGuide#dt4)

There are two distinct types of WFBCCC Investigator Initiated interventional trials based on where patient enrollment occurs. These include:

1) Local WFBCCC Investigator Initiated interventional trials defined as trials where **all patients are enrolled from one of the WFBCCC sites.** These include the main outpatient Cancer Center clinics (located in Winston-Salem) as well as WFBCCC affiliate sites located in Bermuda Run (Davie Medical Center), Clemmons, Lexington, High Point, or Wilkesboro.
2) Multi-Center WFBCCC Investigator Initiated interventional trials defined as trials where patients are enrolled from other sites in addition to WFBCCC sites.
   There are three types of trials that are included in this category:
   a. Trials sponsored by the NCI Community Oncology Research Program (NCORP) that are conducted at multiple sites where the PI is a member of a department at the Wake Forest University Baptist Medical Center.
   b. Trials sponsored by Industry that are conducted at multiple sites and the PI is a member of a department at the Wake Forest University Baptist Medical Center.
   c. Trials sponsored by WFBCCC that are conducted at multiple sites and the PI is a member of a department at the Wake Forest University Baptist Medical Center.

All Adverse Events (AEs) and Serious Adverse Events (SAEs) that occur on any patients enrolled on WFBCCC Investigator Initiated Interventional trials must be entered into the WISER system. The only exception to this requirement is for patients enrolled on NCORP trials at non- WFBCCC sites. AEs and SAEs for NCORP patients enrolled at WFBCCC sites must be entered into the WISER system. Once these AEs and SAEs are entered in WISER, certain actions must be taken regarding the reporting of specific Adverse Events to the DSMC.

All Adverse Events that occur during protocol intervention (defined below) and are coded as either 1) **unexpected grade 4,** 2) **unplanned inpatient hospitalization ≥ 24 hours (regardless of grade)**, or **grade 5 (death)** must be reported to the DSMC to the using the using the SAE console in WISER.

A research nurse or clinical research coordinator when made aware that an adverse event meets one of the above criteria has occurred on a WFBCCC Investigator Initiated interventional trial, is responsible for informing a clinical member of the DSMC by phone (or in-person) about the adverse event. The nurse/coordinator should contact the treating physician prior to calling the DSMC clinical member to obtain all details of the SAE, as well as all associated toxicities to be recorded along with the SAE. In addition, this nurse or coordinator is responsible for entering the adverse event information into the SAE console in WISER. Once the adverse event has been entered into the SAE console an email informing the entire DSMC will be generated.

**THESE REPORTING REQUIREMENTS APPLY TO any staff member on the study team for a WFBCCC Institutional Interventional trial. Ultimately, the protocol PI has the primary responsibility for AE identification, documentation, grading and assignment of attribution to the investigational agent/intervention. However, when an AE event as described above is observed, it is the responsibility of the person who observed the event to be sure that it is reported to the DSMC.**

**What is considered during protocol intervention**?

During protocol intervention is considered to be the time period while a patient is on study treatment or during the time period within 30 days of last study treatment (even if patient begins a new (non-study) treatment during the 30 days). This window of 30 days should be the standard window to be used in all protocols unless a specific scientific rationale is presented to suggest that a shorter window can be used to identify events. If it is a trial sponsored by Industry and the sponsor requires a longer window for monitoring of SAEs, then the longer window of time specified by the sponsor should be followed.

**What is considered as an Unexpected Grade 4 event?**

Any grade 4 event that was not specifically listed as an expected adverse event in the protocol should be considered as unexpected. A grade 4 adverse event can be considered to be unexpected if it is an event that would not be expected based on the treatment being received or if it is unexpected based on the health of the patient. In either case, if there is any uncertainty about whether a grade 4 adverse event is expected or unexpected it should be reported to DSMC.

**DSMC notification responsibilities of the person (e.g., nurse) handling the reporting/documenting of the SAE in WISER:**

1. Make a phone call (or speak in person) to the appropriate clinical member of the DSMC according to the schedule as listed below (page if necessary).
2. Enter a new SAE into the SAE module that is located in the Subject>> CRA Console in WISER WITHIN 24 HOURS of first knowledge of the event. Information can be entered and saved, but the DSMC members will not be notified until a date is entered into the DSMC Notification Date Field. This will ensure that all persons that need to be made aware of the event (i.e., PI, study team members and DSMC members) will be notified; remember to file a copy of the confirmation.
3. Document that the appropriate person(s) on the DSMC has been contacted. Indicate the name of the DSMC clinician that was contacted and the date and time contacted in the Event Narrative

field in the SAE console of the particular subject.

4. Document whether or not the protocol should be suspended based on the discussion with the DSMC clinician. This is the major function of the email notification. Enter whether the protocol should be suspended in the Event Narrative Field.
5. Follow up/update the clinical member(s) of DSMC regarding any new developments or information obtained during the course of the SAE investigation and reporting process.

**Elements needed to complete the SAE form in the Subject Console in WISER (see Screen Shot 3):**

1. Event Date
2. Reported Date
3. Reported by
4. If Grade 5, enter Death Date
5. If Grade 5, enter Death occurred: within 30 days
6. Event Narrative: Brief description (include brief clinical history relevant to this event, including therapies believed related to event). Begin narrative with the DSMC clinician who was notified and Date/Time notified. In addition, state attribution by DSMC clinician as either "Unrelated", "Unlikely", "Possibly", "Probably", or "Definitely". Always include the following here:
    i. DSMC clinician name, date/time contacted and comments
    ii. Date of last dose before the event
    iii. Is suspension of the protocol needed? Y/N
7. Treating Physician comments
8. PI comments, if available
9. Protocol Attribution after discussion with DSMC clinician
10. Outcome (Fatal/Died, Intervention for AE Continues, Migrated AE, Not Recovered/Not Resolved, Recovered/Resolved with Sequelae, Recovered/Resolved without Sequelae, Recovering and Resolving)
11. Consent form Change Required? Y/N
12. SAE Classification ***This is required in order for the email notification to be sent***
13. Adverse Event Details – Enter all details for each AE associated with the SAE.
    a. Course start date
    b. Category
    c. AE Detail
    d. Comments
    e. Grade/Severity
    f. Unexpected Y/N
    g. DLT Y/N
    h. Attributions
    i. Action
    j. Therapy
    k. Click ADD to attach the AE Detail to the SAE.
14. Enter Date Notified DSMC -- ***This is required for the email notification to be sent***
15. Click Submit. The auto-generated notification email will disseminate within 5 minutes. If you do not receive an email within 5 minutes, check that you have entered the "Date Notified DSMC" and the "SAE Classification". If these have been entered and the email still has not been received, take a screen shot of the SAE in WISER and immediately email it out to all of the DSMC members listed

in this SOP. In the subject line, indicate that this is a manual transmission of the SAE in lieu of the auto-generated email. It is required that a notification goes to the DSMC members immediately so that their assessment can be obtained within the 24 hour period requirement. Contact the Cancer Center Programmer/Analyst to alert that there is an issue with the auto-generated email.

**The Clinical Members of DSMC to Notify by Phone or Page:**

| Monday | Tuesday | Wednesday | Thursday | Friday | Saturday | Sunday |
|---|---|---|---|---|---|---|
| Lesser | Hughes | Goodman | Reed | Porosnicu | Seegars | Lesser |
| Hughes | Goodman | Reed | Porosnicu | Seegars | Lesser | Hughes |
| Goodman | Reed | Porosnicu | Seegars | Lesser | Hughes | Goodman |
| Reed | Porosnicu | Seegars | Lesser | Hughes | Goodman | Reed |
| Porosnicu | Seegars | Lesser | Hughes | Goodman | Reed | Porosnicu |
| Seegars | Lesser | Hughes | Goodman | Reed | Porosnicu | Seegars |

**Glenn Lesser, MD** – Hematology Oncology
**Mercedes Porosnicu, MD**-- Hematology Oncology
**Ryan Hughes, MD** – Radiation Oncology
**Michael Goodman, MD** -- Hematology Oncology
**Daniel Reed, MD** -- Hematology Oncology
**Mary Beth Seegars, MD** -- Hematology Oncology

**Definition of Unavailable:**

As a general guideline if the first clinician that is contacted does not respond to the phone call or page within 30 minutes, then initiate contact with the next DSMC clinician listed in the table above on the particular day the SAE is being reported. Allow up to 30 minutes for the new DSMC clinician to respond to a phone call or page before contacting the next member in the table. These times (30 minutes) are a general guideline. Best judgment as a clinical research professional should be used giving considerations of the time of day, severity of the SAE, and other circumstances as to when it is appropriate to contact backup clinicians. If the event occurs near the end of day, then leave messages (voice or email) as appropriate and proceed with submitting the DSMC notification form. It is important to take reasonable steps and to document that some type of contact has been initiated to one or more of the clinical members of DSMC.

**DSMC CLINICAN RESPONSIBILITY:**

It is the responsibility of the DSMC clinician to review all reported events, evaluate the events as they are reported; and communicate a response to the Investigator, event reporter and the members of DSMC. The review will include but not be limited to the information reported; there may be times when additional information is needed in order for an assessment to be made and further communication directly with the investigator may be warranted. DSMC reserves the right to disagree with the Investigator's assessment. If DSMC does not agree with the Investigator, DSMC reserves the right to suspend the trial pending further investigation. If there is any immediate danger or harm that could be present for a future patient based on the information provided in the DSMC report then an immediate suspension of enrollment shouldbe considered.

**AMENDMENTS TO PREVIOUS REPORTS**

If all pertinent information is unavailable with the initial submission, once the additional information is available **do not submit a new report**. Rather, go to the original email that was sent to the DSMC and using that email "reply to all". Entitle this new email "**Amendment** for (list date of event and patient ID)" this will avoid duplications of the same event. List the additional information being reported. This information needs to be entered into WISER as well. To do this, go to the Subject console and click SAEs on the left column. Click on the appropriate SAE number that needs updating. Then click Update. This will allow additional information to be added.

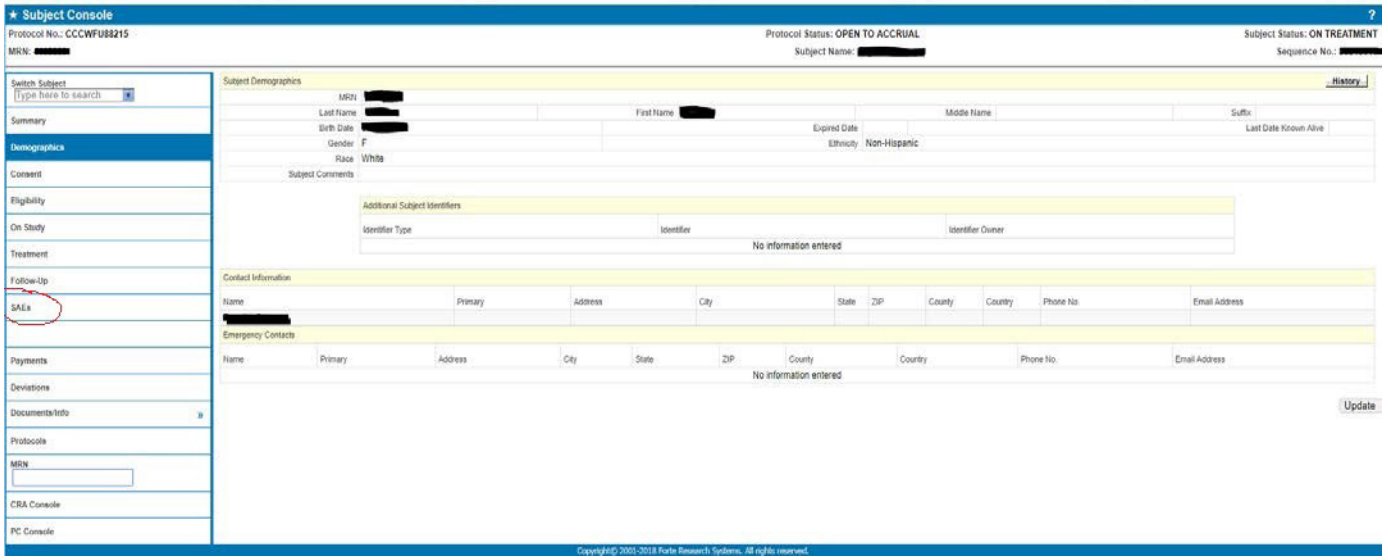
**Acronyms**

**AE** – Adverse Event
**DSMC**-Data and Safety Monitoring Committee
**SAE**-Serious Adverse Event
**WFBCCC** – Wake Forest Baptist Comprehensive Cancer Center
**NCI**-National Cancer Institute
**WISER –**Wake Integrated Solution for Enterprise Research

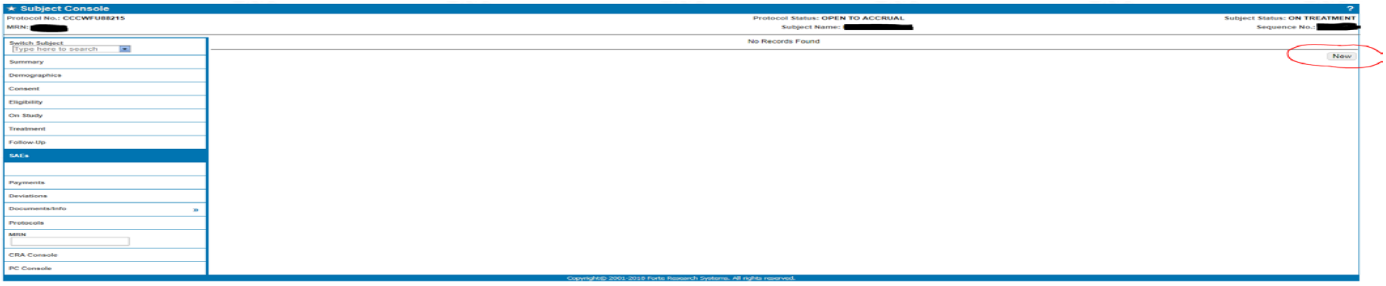
**Screen Shots:**

The following screen shots come from the SAE Console within the Subject Console in WISER.

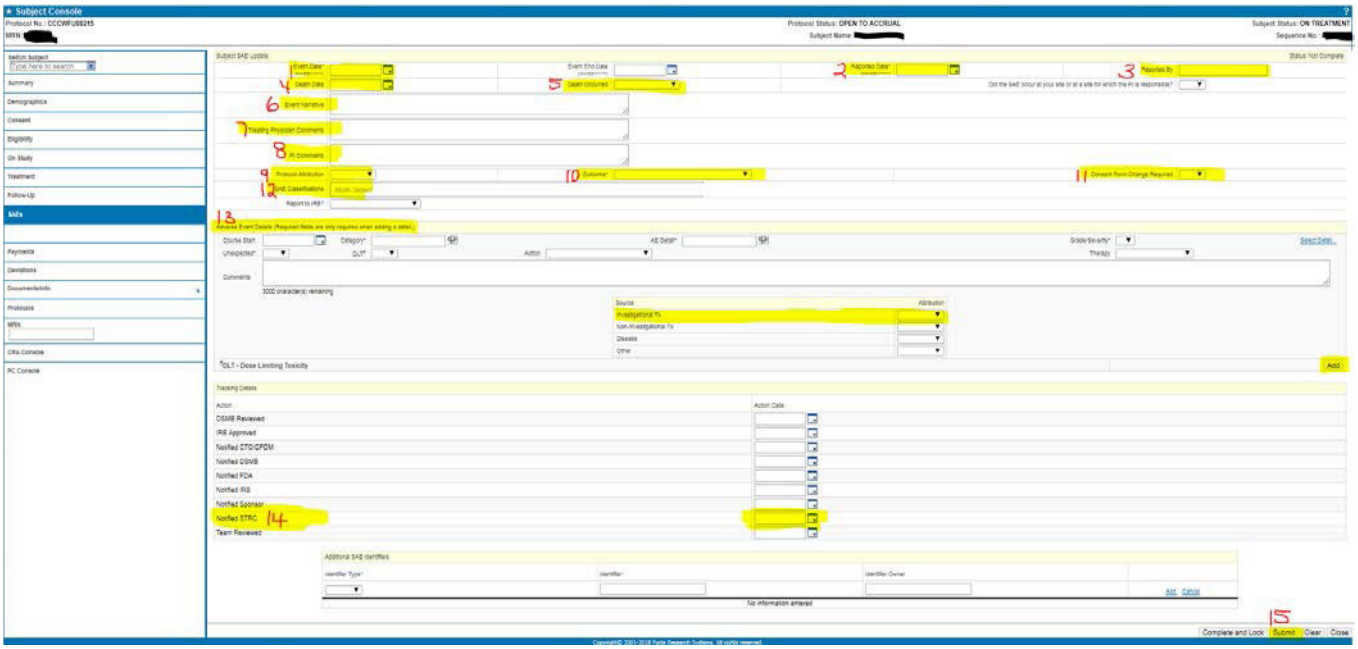
Screen Shot 1:



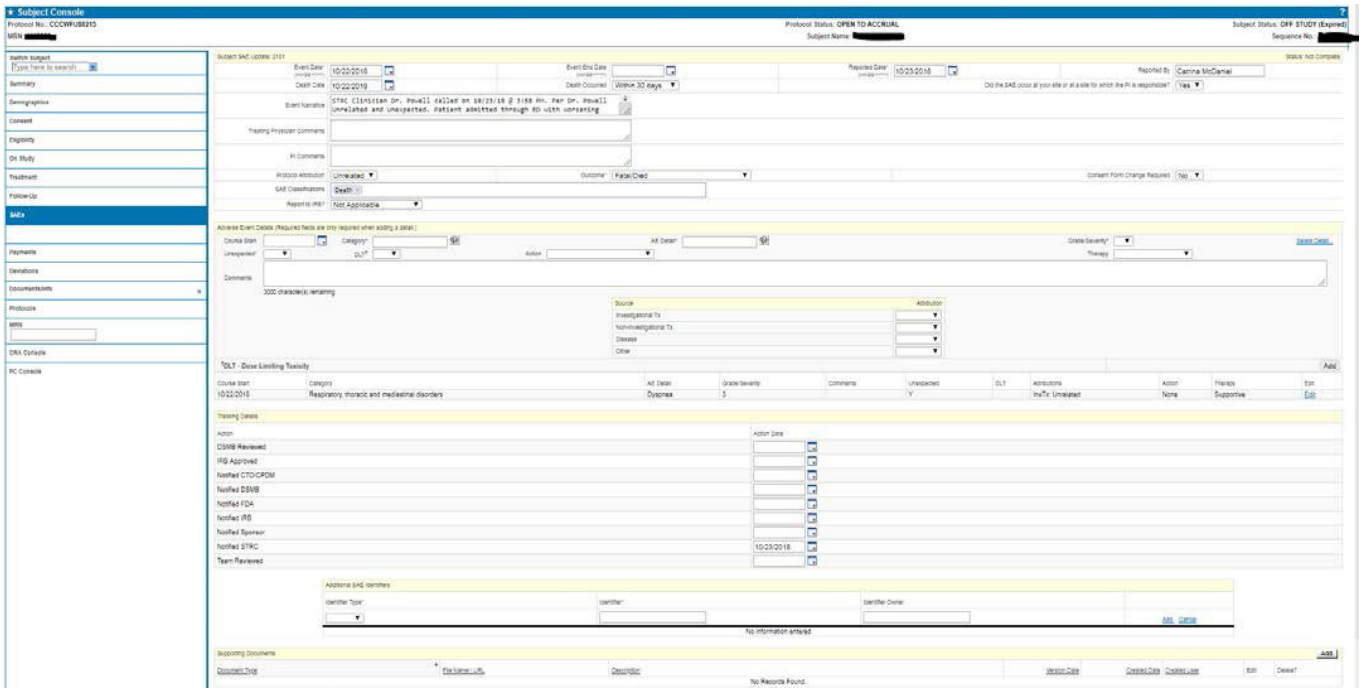

Screen Shot 2:



Screen Shot 3:




Screen Shot 4:



# Appendix D – Off-Study Form

**ORIS Assigned PID: _____ Date: ___ ___ / ___ ___ / ___ ___**

Did the subject meet eligibility criteria for study enrollment? Yes ☐ No ☐

**Reasons for withdrawal**: (*Check all that apply and provide additional information*)

☐ Patient exhibited progression of disease per PET/CT w/ contrast post-cycle 2

☐ Unacceptable toxicity

Describe: _____

☐ Patient withdrawal of consent

☐ Investigator's discretion to withdraw patient from the study because continued participation in the study is not in the patient's best interest

☐ Undercurrent illness: a condition, injury, or disease unrelated to the intended disease for which the study is investigating, that renders continuing the treatment unsafe or regular follow-up impossible

☐ General or specific changes in the patient's condition that renders the patient ineligible for further investigational treatment

☐ Non-compliance with investigational treatment, protocol-required evaluations or follow-up visits

☐ Termination of the clinical trial

☐ Death

Date of death: ___ ___ / ___ ___ / ___ ___

# Appendix E – Data Collection Form

ORIS-assigned PID: _____ Date: ___ ___ / ___ ___ / ___ ___

Post-transplant visit day: ☐ 15 ☐ 30 ☐ 45
☐ 60 ☐ 100 ☐ 6 months post-transplant
☐ 12 months post-transplant

1. Does the patient have clinical evidence of acute GvHD? ☐ Yes ☐ No

   If yes:

   What is the patient's organ stage (as per criteria in Appendix F):

   ☐ Stage 0

   ☐ Stage 1

   ☐ Stage 2

   ☐ Stage 3

   ☐ Stage 4

   What is the patient's IBMTR grade of acute GvHD (as per criteria in Appendix F):

   ☐ Stage 0

   ☐ Stage 1

   ☐ Stage 2

   ☐ Stage 3

   ☐ Stage 4

2. Has the subject relapsed? ☐ Yes ☐ No
   If yes, date of relapse: ____/____/____

If GVHD is present, answer the following questions:

3. Did the subject experience 50% body surface of skin involvement? ☐ Yes ☐ No

4. Did the subject experience elevated bilirubin? ☐ Yes ☐ No

   Bilirubin value: _____ mg/dL Date of bilirubin lab: ____/____/____

5. Was there a progressive onset of cGvHD? ☐ Yes ☐ No

6. Did the subject experience thrombocytopenia? ☐ Yes ☐ No

   Platelet value: _____ mcL Date of platelet lab: ____/____/_____

7. Was there gut involvement? ☐ Yes ☐ No

8. Karnofsky performance status:

   ☐ 100 Normal no complaints: no evidence of disease.
   ☐ 90 Able to carry on normal activity: minor signs or symptoms of disease.
   ☐ 80 Normal activity with effort: some signs or symptoms of disease.
   ☐ 70 Cares for self: unable to carry on normal activity or to do active work.
   ☐ 60 Requires occasional assistance, but is able to care for most personal needs.
   ☐ 50 Requires considerable assistance and frequent medical care.
   ☐ 40 Disabled; requires special care and assistance.
   ☐ 30 Severely disabled; hospital admission is indicated although death not imminent.
   ☐ 20 Very sick: hospital admission necessary; active supportive treatment necessary.
   ☐ 10 Moribund; fatal processes progressing rapidly.
   ☐ 0 Dead

9. Was the subject still receiving corticosteroids at the time of cGvHD diagnosis?

   ☐ Yes ☐No

10. Was there an absence of early response to immunosuppression? ☐ Yes ☐ No

# Appendix F – Acute GVHD Clinical Criteria

**Organ Stages of Acute GVHD**

| Stage | Skin<br>Percent BSA | Liver<br>Bilirubin | Gut<br>Stool Volume |
|---|---|---|---|
| 0 | 0 | < 2.0 | ≤ 500 |
| 1 | <25 | 2.0 – 2.9 | >500* |
| 2 | 25 – 50 | 3.0 – 5.9 | >1000 |
| 3 | >50 | 6.0 – 14.9 | >1500 |
| 4 | Bullae | ≥ 15.0 | >2000† |

*or persistent anorexia, nausea and vomiting
†or severe abdominal pain with or without ileus

Glucksberg et.al. Transplantation 1974; 18:295-304
Thomas et.al. New Engl J Med 1975; 292:895-902
Przepiorka et.al. Bone Marrow Transplant 1996; 15: 825-828

**MAGIC Grading of Acute GvHD**

| Stage | Skin (Active Erythema Only) | Liver (Bilirubin) mg/dl | Upper GI | Lower GI (Stool Output/Day) |
|---|---|---|---|---|
| 0 | No active erythematous GVHD rash | < 2 | No or intermittent nausea, vomiting or anorexia | Adult: < 500 mL/day or < 3 episodes/day |
| 1 | Maculopapular rash < 25% BSA | 2-3 | Persistent nausea, vomiting or anorexia | Adult: 500-999 mL/day or 3-4 episodes/day |
| 2 | Maculopapular rash 25%-50% BSA | 3.1-6 | - | Adult: 1000-1500mL/day or 5-7 episodes/day |
| 3 | Maculopapular rash > 50% BSA | 6.1-15 | - | Adult: > 1500 mL/day or > 7 episodes/day |
| 4 | Generalized erythroderma (> 50% BSA) plus bullous formation and desquamation > 5% BSA | > 15 | - | Severe abdominal pain with or without ileus or grossly bloody stool (regardless of stool volume) |

# Appendix G – Survival Form

**Study Number: ___ ___ ___ ___ ___ PID: ___ ___ ___ ___ ___ ___ ___ ___**

**PI: _____ Date (mm/dd/yyyy): ___ ___/___ ___/___ ___ ___ ___**

**Instructions:**

1. Last known Survival Status:
   - ☐ Alive
   - ☐ Dead
   - ☐ Lost to Follow-up

2. Expired Date: __/__/____

   - ☐ Relapse Mortality
   - ☐ Non-Relapse Mortality
     - ☐ GVHD
     - ☐ Infection
     - ☐ Other: Specify _____

3. Last known Alive Date: __/__/____

4. Survival Status source: _____
   *Instructions: Source can be EMR, obituary, family member etc. Add to comments in wiser follow-up section*

5. Comment:

_____
_____
_____
_____

Haploidentical Stem Cell Transplant using Post Transplant Cyclophosphamide for GvHD Prophylaxis: A Pilot Study
Comprehensive Cancer Center of Wake Forest University
CCCWFU # 97214
ClinicalTrials.gov; NCT02248597

# Appendix H – Adverse Event Log

## Appendix G –CCCWFU 97214 Adverse Event Log

**PI: _____** **Subject PID: _____** **MRN: _____**
**Cycle #:** **Cycle Start Date:** **Cycle Start Time:** **Cycle End Date:** **Cycle End Time:**

| **Adverse Event CTC Term** | **Lab Value** | **Grade** (1-5) per CTC | **Start Date** | **Attribution** DEF= Definite PROB= Probable POSS= Possible UNLK= Unlikely UNRL= Unrelated | **Treating MD Initials + Date** | **End Date** | **Expected** N= No Y= Yes | ***Serious Adverse Event Detail:** NO= No LT= Life Threatening DTH= Death DIS= Disability HOS= Hospitalization CA= Caused congenital anomaly RI= Required intervention to prevent impairment | **Dose Limiting Toxicity (DLT)** N= No Y= Yes | **Action Taken** NO= None DR= Dose Reduced RI= Regimen Interrupted TD= Therapy discontinued INTR= Interrupted then reduced | **Therapy Given** NO= None SYM= Symptomatic SUP= Supportive VSUP= Vigorous Supportive | **Reportable?** IRB= IRB STRC= STRC FDA= FDA SPON= Sponsor (Mark all that apply) | **Adverse Event Report (AER) filed?** N= No Y= Yes | **Outcome** R= Recovered TX= Still under treatment or observation A= Alive with Sequalae D= Died |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
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*Serious Adverse Event: Hospitalization; Disability; Birth Defect; Life-threatening; Death.

CTCAE Version 4 - http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

STRC = Safety and Toxicity Review Committee

Version
10/30/17