

**Viral Specific T-Lymphocytes by Cytokine Capture System (CCS) to  
Treat Infection with Adenovirus, Cytomegalovirus or Epstein-Barr  
Virus after Hematopoietic Cell Transplantation or Solid Organ  
Transplantation and in Patients with Compromised Immunity**

July 21, 2022

**Principal Investigator/Protocol Chair**

Jessie Barnum, MD

Division of Blood and Marrow Transplantation and Cellular Therapies

Children's Hospital of Pittsburgh of UPMC

4401 Penn Avenue, Plaza Building, 4th Floor

Pittsburgh, PA 15224

[REDACTED]

[REDACTED]

## Co-Investigators

Kathleen Dorritie, MD  
Division of Hematology/Oncology  
5115 Centre Avenue, [REDACTED]  
Pittsburgh, PA 15232  
(412) 864-6600  
[REDACTED]

Paulina Horvei, MD  
Division of Blood and Marrow Transplantation  
and Cellular Therapies  
Children's Hospital of Pittsburgh of UPMC  
4401 Penn Avenue, Plaza Building, [REDACTED]  
Pittsburgh, PA 15224  
[REDACTED]

Marian Michaels, MD, MPH  
Division of Pediatric Infectious Diseases  
Children's Hospital of Pittsburgh of UPMC  
4401 Penn Avenue, [REDACTED]  
Pittsburgh, PA 15224  
[REDACTED]

Fernanda Silveira, MD  
Division of Infectious Diseases  
Falk Medical Building, [REDACTED]  
3601 Fifth Avenue  
Pittsburgh, PA 15213  
[REDACTED]

Puneet Sood, MD  
Division of General Internal Medicine  
UPMC Montefiore  
3459 Fifth Avenue, [REDACTED]  
Pittsburgh, PA 15213  
[REDACTED]

Randy Windreich, MD  
Division of Blood and Marrow Transplantation  
and Cellular Therapies  
Children's Hospital of Pittsburgh of UPMC  
4401 Penn Avenue, Plaza Building, [REDACTED]  
Pittsburgh, PA 15224  
[REDACTED]

Rafic Farah, MD  
Division of Hematology/Oncology  
5115 Centre Avenue, [REDACTED]  
Pittsburgh, PA 15232  
(412) 864-6600  
[REDACTED]

Annie Im, MD  
UPMC Hillman Cancer Center  
Division of Hematology/Oncology  
5115 Centre Avenue, [REDACTED]  
Pittsburgh, PA 15232  
(412) 864-6600  
[REDACTED]

George Mazariegos, MD  
Division of Pediatric Transplantation  
Children's Hospital of Pittsburgh of UPMC  
4401 Penn Avenue, [REDACTED]  
Pittsburgh, PA 15224  
[REDACTED]

Rakesh Sindhi, MD  
Division of Pediatric Transplantation  
Children's Hospital of Pittsburgh of UPMC  
4401 Penn Avenue, [REDACTED]  
Pittsburgh, PA 15224  
[REDACTED]

Paul Szabolcs, MD  
Division of Blood and Marrow Transplantation  
and Cellular Therapies  
Children's Hospital of Pittsburgh of UPMC  
4401 Penn Avenue, Rangos Building, [REDACTED]

### **Study Contacts: Laboratories**

#### **Graft Processing**

Albert Donnenberg, PhD  
Children's Hospital of Pittsburgh of UPMC  
Hematopoietic Stem Cell Laboratory  
One Children's Hospital Drive  
4401 Penn Avenue, Rangos Building  
Pittsburgh, PA 15224  
[REDACTED]

#### **Mechanistic Studies**

Paul Szabolcs, MD  
Division of Blood and  
Marrow Transplant and Cellular Therapies  
Children's Hospital of Pittsburgh of UPMC  
4401 Penn Avenue, Rangos Building, 5th Floor, [REDACTED]  
Pittsburgh, PA 15224  
[REDACTED]

## **1.0 STUDY OBJECTIVES, SPECIFIC AIMS, BACKGROUND AND SIGNIFICANCE**

### **1.1 Objective**

#### **1.1.1 Primary Objective**

The primary objective of this Phase I/II prospective clinical trial is to determine the feasibility, safety and efficacy of administering partially matched viral specific T cells to mediate antiviral activity in hematopoietic cell transplantation (HCT) and solid organ transplantation (SOT) recipients and/or patients with compromised immunity with viral reactivation or infection. We will closely monitor these patients for infusion reactions and monitor the effects of these cells on graft-versus-host disease (GVHD).

#### **1.1.2 Secondary Objective**

Secondary objectives are to monitor the durability and kinetics of viral load following viral specific T cell infusion.

### **1.2 Specific Aims**

#### **1.2.1 Hypothesis**

Viral specific T cells will be well tolerated, safe, and efficacious for patients with adenovirus, CMV or EBV viremia and/or disease.

#### **1.2.2 Primary Specific Aim**

To determine whether viral specific T cells are safe and efficacious against adenovirus, cytomegalovirus (CMV), and Epstein-Barr virus (EBV). We will evaluate all infused products for sterility, purity, cell dose, assess CD4+/IFN-gamma and CD8+/IFN-gamma content.

#### **1.2.3 Secondary Specific Aim**

To evaluate viral load disease burden by imaging and symptomatology, and overall survival.

### **1.3 Background and Rationale**

#### **1.3.1 Clinical Significance of Viral Infections**

During the period of immunodeficiency after HCT and SOT, viral infections are an important cause of morbidity and mortality. The degree of risk for infection is dependent upon the degree of immunosuppression, type of graft source, degree of graft manipulation, and the immune status of the donor. Reactivation or primary infection with viruses such as adenovirus, CMV, and EBV are a serious cause of morbidity and mortality after transplant. Antiviral medications have efficacy in only some of these viruses, and can precipitate organ toxicity and morbidity (Mohty et al., 2003). Patients with compromised immunity, especially those with primary immunodeficiency and those with treated with ongoing immunosuppression, are also vulnerable to these infections. A recent publication cites the use of antiviral T cells in patients with severe combined immunodeficiency as a bridge to transplant (Miller, 2018). Since a delay in recovery of virus-specific cellular immune response is clearly associated with viral reactivation and disease, cellular immunotherapy to restore viral-specific immunity is an attractive option that has been applied to target these viruses.

### **1.3.2 Cytomegalovirus (CMV)**

Cytomegalovirus is a lytic virus that usually causes an asymptomatic infection in immunocompetent individuals. It persists in a latent state in approximately 70% of healthy adults and replicates in epithelial cells, fibroblasts and monocytes. Reactivation of CMV in the stem cell recipient can result in significant morbidity and mortality, with clinical manifestations including fevers, interstitial pneumonitis, gastroenteritis, hepatitis, encephalitis and retinitis (Boeckh et al., 2003). Cell-mediated immunity is considered the most important factor in controlling CMV infection and CMV-specific CD4+ and CD8+ lymphocytes play an important role in immune protection. Ganciclovir and foscarnet have been shown to decrease morbidity and mortality in patients who have CMV disease, but they have significant side effects, particularly marrow suppression and nephrotoxicity, respectively.

### **1.3.3 Epstein-Barr Virus (EBV)**

Epstein-Barr virus is a gamma herpes virus that infects more than 95% of the world's population. Primary infection usually produces a mild self-limiting disease, which is followed by latent infection in B cells and productive replication in B cells and mucosal epithelium. In immunocompromised hosts, outgrowth of B cells may lead to the development of post-transplant lymphoproliferative disease (PTLD). The overall incidence of PTLD after HCT is less than 1-2%, but the incidence is increased in recipients with an underlying diagnosis of immunodeficiency and for recipients of stem cells from unrelated or human-leukocyte-antigen (HLA)-mismatched donors who receive grafts that are selectively depleted of T cells to prevent graft-versus-host disease (GVHD) (Cohen et al., 2007; Curtis et al., 1999; Young & Rickinson, 2004). In SOT, the incidence of PTLD varies according to several risk factors including type of transplant, age of recipient, and duration and type of immunosuppression therapy. PTLD development after SOT is estimated from 1-20%, with the highest incidence reported in intestinal and multivisceral transplants (5-20%) followed by lung and heart transplants (2-10%), followed by renal and liver transplants (1-5%) (Brunstein et al., 2006).

Few small molecule drugs have any effect on B cells already transformed by EBV, although nucleoside analogs, like ganciclovir, do inhibit its replicative cycle. Chemotherapy is rarely effective and associated with significant toxicity. One option for prophylaxis and treatment of PTLD after HSCT is rituximab, a monoclonal antibody against CD20. Response rates to rituximab between 55% and 100% have been reported in different series (Brunstein et al., 2006; Cohen et al., 2007; Kuehnle et al., 2000). However, not all patients respond and rituximab depletes normal B-cells for many months. This can be problematic in a patient population that is already immunosuppressed.

### **1.3.4 Adenovirus**

Adenovirus is a lytic DNA virus that is highly contagious, living at room temperature for up to 3 weeks in certain fomites (Echavarria, 2008). There are 52 known serotypes of adenovirus, forming six distinct species (A to F), which differ in their tissue specificity and virulence. Infections with adenovirus are frequent in childhood, and in healthy individuals they are self-limited illnesses that induce serotype-specific immunity. Adenovirus infection is a significant cause of morbidity and mortality in immunocompromised individuals, in whom it may produce pneumonia, hemorrhagic cystitis, nephritis, colitis, hepatitis, pancreatitis and meningoencephalitis. Adenovirus has a particularly high incidence (up to 40%) after pediatric HSCT (Myers et al., 2005). Several reports have shown that clearance of adenovirus infection is associated with detection of adenovirus specific T cells (Feuchtinger et al., 2005; Myers et al., 2007). Cidofovir is most frequently used for treatment, but its significant nephrotoxicity is an important concern and limitation to its utility.

### **1.3.5 Adoptive Immunotherapy with Viral-Specific T-lymphocytes obtained after enrichment with IFN $\gamma$ capture from healthy donors (also known as “Gamma capture”)**

Antiviral adoptive immunotherapy induces a virus-specific T-cell response in the patient following the infusion of T cells. The method we will utilize is ex-vivo stimulation of T cells by exposing healthy donor T cells to protein from the virus, enrichment of the sample for the interferon gamma-secreting cells, then “capture” and infusion of the IFN- $\gamma$  cells. This method has been previously performed with success and safety. Recent studies will be summarized herein:

#### **1.3.5.1 Adenovirus**

Feuchtinger T et al. Isolation and expansion of human adenovirus-specific CD4+ and CD8+ T cells according to IFN- $\gamma$  secretion for adjuvant immunotherapy. *Experimental Hematology* 2004, 32, 282-289.

A clinical grade protocol was established in which isolated cells were expanded for a median of 18 days using IL-2 and an autologous feeder cell stimulation in culture. This proof of principle study demonstrated that adenovirus-specific T cells had specific effector functions, as shown by intracellular cytokine staining, cytotoxicity and Elispot assays.

Feuchtinger T et al. Safe adoptive transfer of virus-specific T-cell immunity for the treatment of systemic adenovirus infection after allogeneic stem cell transplantation. *British Journal of Haematology* 2006, 134, 64-76.

In this study, the CliniMACS™ and Cytokine Secretion System (CCS) (both by Miltenyi Biotec) were utilized, which significantly decreased the time of culture and stimulation to 16 hours. Nine children received virus-specific donor T cells. Adoptive transfer was successful in 5 of 6 evaluable patients. In 4 of the 5 cases with successful adoptive transfer, adenovirus was cleared from the blood. One patient with preexisting chronic GVHD experienced skin GVHD following immunotherapy, which responded to steroids.

Feuchtinger T et al. Clinical grade generation of hexon-specific T cells for adoptive T-cell transfer as a treatment of adenovirus infection after allogeneic stem cell transplantation. *Journal of Immunotherapy* 2008, 31, 199-206.

This translational study provides important laboratory-based data that their adenovirus-specific T cell product had a mixed population of CD4 and CD8 positive T cells with an intermediate effector memory phenotype. Type 5 hexon protein was used for stimulation, and there was good cross-reactivity against viral strains from other adenovirus species. In this cohort of 76 healthy donors screened, 72.4% had a detectable hexon-specific T-cell response. When CTL purification was attempted in the GMP setting it was successful in 12 of 12 healthy donors.

Feucht et al. Adoptive T-cell therapy with hexon-specific Th1 cells as a treatment of refractory adenovirus infection after HSCT. *Blood* 2015, 125, 1986-1994.

In this recent publication, the authors report their clinical trial results of 30 patients with adenoviral disease or viremia who received adenovirus-specific T cells. In this cohort, 86% of patients with antigen-specific responses had complete clearance of viremia. The T cells were haploidentical in 57% of cases. In the 8 weeks following immunotherapy, only 7% of patients had grade 1 GVHD, and no patients developed grade 2-4 GVHD.

Qian C et al. Curative or pre-emptive adenovirus-specific T cell transfer from matched unrelated or third party haploidentical donors after HSCT, including UCB transplantations: a successful phase I/II multicenter trial, *Journal of Hematology and Oncology* 2017, 10:102.

In this study of adults and children post-HCT, 10 of 11 patients (91%) achieved clearance of adenovirus 14-180 days after receiving adenovirus-specific T cells. Ten of 11 patients had adenoviral disease (9 gastrointestinal and 1 pulmonary), and 90% of these patients experienced complete resolution of ADV symptoms. Six of the 11 adenovirus-specific T cell products were obtained from haploidentical donors; all of these patients were recipients of an umbilical cord blood graft. Three patients experienced reactivation of acute GVHD within 30 days of the infusion, all of these patients had GVHD prior to ADV-specific T cells, one patient grade III and two had grade II. Of note, immunosuppression was discontinued in 2 of the patients prior to the infusion of ADV-specific cells. Nine of 11 patients were alive at 6 months after ADV-VST. One died of bacterial sepsis on day +132 after ADV-VST and one died of disseminated adenovirus disease.

#### **1.3.5.2 CMV**

Feuchtinger T et al. Adoptive transfer of pp65-specific T cells for the treatment of chemorefractory cytomegalovirus disease or reactivation after haploidentical and matched unrelated stem cell transplantation, *Blood* 2010, 116, 4360-4367.

In this study utilizing IFNg capture after CMV pp65-stimulation CTL was administered to 18 patients after haploidentical or matched unrelated donor HCT. There was an 83% response rate without GVHD or acute side effects.

#### **1.3.5.3 EBV**

Icheva V et al. Adoptive transfer of Epstein-Barr virus (EBV) nuclear antigen 1-specific T cells as treatment for EBV reactivation and lymphoproliferative disorders after allogeneic stem-cell transplantation. *Journal of Clinical Oncology* 2013, 31, 39-48

In this study, the authors report on EBNA-1-specific T cells that were given to 10 pediatric and adult patients with EBV viremia and/or PTLD after HSCT. There was no acute toxicity, and no more than grade 2 GVHD. Virologic response was achieved in 70% of patients.

### **1.3.6 Institutional Experience Miltenyi CCS on Single Case IND/eIRB Treatment Plans**

EG is a baby who was diagnosed with pre-symptomatic Tay Sachs disease (B1 variant) and received reduced intensity conditioning with alemtuzumab, hydroxyurea, fludarabine, thiotepea and melphalan, followed by a 6/6 antigen (7/8 allele) matched unrelated cord blood transplant on 10/29/2013 at the age of 6 months. He had low level adenoviremia which increased to >23,000 copies/mL by day +13. He received many doses of cidofovir and DLI from the cord (5.6 e5/kg CD3/kg) on 12/6/2013 and high loads of adenoviremia persisted. The patient's haploidentical mother underwent donor evaluation and leukopheresis and the patient received adenoviral-specific interferon gamma enriched T cells on 1/23/2014, 2/12/2014 and 2/17/2014. The patient received additional adenoviral-specific interferon gamma enriched T cells from whole blood on 3/7/2014. The patient suffered a neurologic

decompensation thought to be related to a progressive metabolic degenerative process and died on 5/2/2014. Despite cidofovir, maternal adenoviral-specific T cells, brincidofovir and further cidofovir, EG disseminated adenoviral infection persisted. Adenovirus PCR prior to death was 3.2 million copies/mL, and autopsy showed disseminated adenovirus with adenoviral inclusions in his pancreas, lungs, and liver.

CJ is a 3-year boy with FLT3-ITD positive AML who experienced graft failure despite 4 allogeneic transplants. He developed adenoviremia with >100,000 copies/mL with no response to cidofovir. He received a fresh infusion on 9/13/2016 and a frozen infusion on 10/14/2016. He died on 11/2/2016, and autopsy showed disseminated adenovirus.

MF is 40-year old female with common variable immunodeficiency with a history of multiple lung infections and bronchiectasis, leading to end-stage lung disease. She underwent bilateral orthotopic lung transplant in August 2016, which was complicated by multiple episodes of rejection. She underwent cadaveric bone marrow transplant from the same lung donor under IND15414 on 10/19/2017 and 10/20/2017. One week post-BMT, she developed diarrhea, which prompted stool studies and she was found to have adenoviral enteritis. She received two doses of weekly cidofovir, though acute on chronic renal insufficiency prompted a change to brincidofovir. Adenoviremia continued, and there was concern for impending graft failure, thus she received donor lymphocyte infusions on 11/9/2017 and 11/22/2017. She received adenoviral specific T cells from her brother on 11/16/2017 and from her nephew on 2/13/2018 with a viable IFN $\gamma$ +CD3+ T cell dose of  $5.54 \times 10^5$ . The patient's adenoviral copy number became undetectable following the second antiviral infusion. She did develop GVHD but donor lymphocyte infusions complicated her clinical picture. She died of fungal septic shock with multisystem organ failure on 4/24/2018.

EM is a 3 year old female with Krabbe disease who underwent a matched unrelated cord blood transplant. Following alemtuzumab and chemotherapy, she experienced adenovirus enteritis and viremia with up to 15,900 copies/mL beginning on day +23. She also had CMV viremia beginning the day of transplant which increased to 3,091 IU/mL. These viral infections persisted despite treatment with cidofovir, foscarnet, ganciclovir and Cytogam. She received CMV and adenovirus-specific T cells from her father without issue. Her viral infections were both in remission 17 days post infusion.

KF is a 17-year old male with dyskeratosis congenita and associated bone marrow failure. He underwent a matched unrelated bone marrow transplant on 8/13/2019. He achieved 100% donor engraftment and had an uncomplicated course until he suffered gastrointestinal graft-versus-host disease of the GI tract on day +111 in the context of medication nonadherence. His GVHD responded to steroid therapy which was gradually weaned. On day +149 he developed adenoviremia with 9,340 copies/mL which increased and was persistently >560,000 copies/mL in spite of weekly cidofovir. Adenovirus was also detected in his urine and stool. He received adenovirus specific T cells from his mother. The adenovirus copies in his blood decreased to <200-350 copies 4 days post-infusion, and cleared from the blood, urine and stool by 46 days post infusion.

Patient, #infusion	Date of infusion	Source of cells	Viable CD3 cells/kg	CD4 IFN $\gamma$ + (%)	CD8 IFN $\gamma$ + (%)	Culture results	Infusion reactions	GVHD	Viability (%)
EG, #1	1/23/2014	Maternal haplo-	10,000	20.8	39.7	No growth	None	None	54

		fresh apheresis							
EG, #2	2/12/2014	Maternal haplo-frozen (thaw & wash)	360,000	20.8	39.7	No growth	None	None	64
EG, #3	2/17/2014	Maternal haplo-frozen (thaw)	39,600	20.8	39.7	No growth	None	None	45
EG, #4	3/7/2014	Whole blood	13,500	27.8	10	No growth	None	None	50
CJ, #1	9/14/2016	Maternal haplo – fresh	168,000	15.1	3.9	No growth	None	None	70
CJ, #2	10/14/2016	Maternal haplo-frozen (wash, then selected)	9,030	1.5	0.1	No growth	None	None	76
MF, #1	11/16/2017	Brother, haplo - fresh	13,700	2.9	9.3	No growth	None	Yes Lower GI GVHD bx proven 12/15/17	68.4
MF, #2	2/13/2018	Nephew, haplo-fresh	29,600	55.6	42.2	No growth	None	Skin GVHD by exam 2/26/18, bx proven 3/5/18	43.7
EM	5/24/2019	Father, haplo-fresh	100,000	6.4	21.3	No growth	None	None	89.5
KF	1/23/2020	Mother, haplo-fresh	371	26.9	15.4	No growth	None	None	68.2

## 2.0 RESEARCH DESIGN AND METHODS

### 2.1 Classification and Methodological Designs

This is a phase I/II, single center clinical trial designed to evaluate whether partially matched viral specific T cells are safe and efficacious against adenovirus, CMV, and EBV.

## **2.2 Detailed Description of Study Design**

### **2.2.1 Study Design**

The primary purpose of this phase I/II study is to evaluate whether partially matched,  $\geq 2/6$  HLA-matched, viral specific T cells have efficacy against adenovirus, CMV, and EBV, in subjects who have previously received any type of allogeneic HCT or solid organ transplant (SOT), or have compromised immunity. Reconstitution of anti-viral immunity by donor-derived cytotoxic T lymphocytes has shown promise in preventing and treating infections with adenovirus, CMV, and EBV. However, the weeks taken to prepare patient-specific products, and cost associated with products that may not be used limits their value. In this trial, we will evaluate viral specific T cells generated by gamma capture technology. Eligible patients will include HCT and/or SOT recipients, and/or patients with compromised immunity who have adenovirus, CMV, or EBV infection or refractory viremia that is persistent despite standard therapy. Infusion of the cellular product will be assessed for safety and efficacy.

Eligible subjects will receive  $\leq 1 \times 10^5$  (100,000) CD3 cells/kg (minimum of  $1 \times 10^2$  CD3 cells/kg).

If at Day 14 post-infusion, a subject shows a partial response, defined as a decrease in viral load of at least 50% from baseline or 50% improvement of clinical signs and symptoms, or no response, they are eligible to receive up to 4 additional cellular infusions from the same donor, at a minimum of 14-day intervals. If the same donor is no longer available, eligible or appropriate, another donor may be considered for a maximum of 4 total cellular infusions at the discretion of the study PI and treating physician. A subject will not exceed a maximum of 5 total infusions from 2 donors.

If at Day 14 post-infusion, a subject shows a complete response, defined as return to normal range defined by specific assay used and clinical signs and symptoms, subject will be followed according to Appendix 1: Schedule of Events.

Subjects are followed for 1 year post initial viral-specific T cell infusion. If subjects receive additional infusion(s), GvHD and adverse events will be followed for an additional 90 days from last infusion. Data may be abstracted from subjects' medical charts for an additional 1 year after most recent viral-specific T cell infusion.

### **2.2.2 Screening/Baseline Visit**

Screening will begin once informed consent is obtained. During the screening period, the patient's medical record will be reviewed for past and current medical history, a physical exam will be performed, and any necessary lab work/study procedures will be performed as outlined in the Schedule of Events (Appendices 1 and 2). Some of the assessments may have been conducted as a part of their routine clinical care and the results may be used if they fall within an acceptable window as outlined in the Schedule of Events.

### **2.2.3 Follow-up Visits Post Viral-Specific T Cell Infusion**

Following the infusion, study visits will align with routine, standard of care practices. Medical records may be reviewed and information may be collected for research purposes. All assessments and tests, with the exception of the research blood collection, are considered standard of care. Assessments may include but are not limited to those listed below.

- Physical exams

- Lab work
- Adverse Events
- Concomitant medications
- Research blood collection

#### **2.2.4 Visit Windows**

Study visits, with designated windows, are indicated in the Schedule of Events (see Appendices 1 and 2).

### **2.3 Investigational Intervention**

#### **2.3.1 Donor Evaluation, Screening and Selection**

Eligibility and suitability for donation will be evaluated by a provider who is knowledgeable of the donation procedure. This person will be someone other than the recipient's primary transplant physician. The donor completes a health screening questionnaire according to current FACT standards with the inclusion of CJD and Zika risk factors. The donor's provider obtains a medical history, review of systems and physical examination.

The following testing will be obtained on all donors (more than one donor can be screened at one time):

- Complete blood count and differential
- Basic metabolic panel
- Hepatic function panel
- Infectious disease markers; anti-CMV, hepatitis B surface antigen, hepatitis B core antigen, anti-hepatitis C, HIV PCR NAT, anti-HIV1, anti-HIV2, hepatitis B NAT, hepatitis C NAT, WNV NAT, anti-HTLV I and II, treponema palladium
- If deemed necessary, EBV serologies (EBV panel), testing for adenovirus- specific immunity, or other viral immunity testing
- Blood type and screen
- HLA typing (if not already obtained)
- Pregnancy test (urine)

#### **2.3.2 Processing of Viral Specific T-Lymphocytes**

Peripheral blood mononuclear cells will be collected from the donor and loaded onto our Miltenyi Biotec CliniMACS Prodigy® or CliniMACS® Plus where they will be stimulated in vitro with viral-specific antigen(s). The cells are then immunomagnetically labeled with interferon gamma via the cytokine capture system. By this method, viral specific, gamma-secreting T cells, are captured in a closed, sterile system.

#### **2.3.3 Product Release Criteria for Infusion**

- The following product release criteria must be met in order to proceed with the infusion of viral specific T-lymphocytes:
  - Gram Stain Negative
  - Endotoxin < 5.0 EU/kg
  - Cell dose up to  $1 \times 10^5$  (100,000) CD3 cells/kg

#### **2.3.4 Pre-Medications Prior to Viral-Specific T Cell Infusion**

Subjects will be pre-medicated, prior to their infusion, based upon institutional guidelines.

Diphenhydramine 1 mg/kg (max 50 mg) PO or IV and acetaminophen 15 mg/kg (max 650 mg) (or acceptable alternative) PO or IV 30-60 minutes prior to infusion is recommended.

### **2.3.5 Infusion of Viral Specific T-Lymphocytes**

Infusion will be completed per institutional guidelines and will ideally occur within 1.5-4 hours after cell processing has been completed.

An aliquot of the cellular product will be sent for 14-day sterility testing. If cultures become positive, the subject will be started on appropriate broad-spectrum antibiotics with consultation from the infectious disease service as needed.

### **2.3.6 Graft-versus-Host Disease (GVHD) Prophylaxis, Diagnosis and Treatment**

GVHD prophylaxis will be based upon subject protocol or standard of care. The diagnosis and treatment of GVHD will be based on current institutional guidelines. It is anticipated that most subjects will be receiving at least one Immunosuppressive agent and more as clinically indicated.

### **2.3.7 Mechanistic Assays: Acquisition of Immune Competence and Analysis of the Immune Repertoire**

Testing for immune reconstitution will be performed from peripheral blood.

Lymphocyte subsets, including percentage and absolute numbers of CD3+, CD4+, CD8+, CD19+, and CD16/56+ cells along with antigen presenting monocyte and dendritic cell subsets may be monitored by flow cytometry. Developmental stages of major T and B lymphocyte subsets may be determined. Assessment of functional thymic recovery and output may also be tested by multiparameter flow cytometry for naive, central memory, effector memory phenotypes, including regulatory T-cells (Treg). Cell turnover in subsets may be measured by staining for intracellular markers of proliferation and apoptosis.

TREC assay, sequence based TCRVbeta repertoire assays may aid to determine the tempo and quality of thymopoiesis in conventional T cells and Tregs. Clonal fluctuations in repertoire may be examined and correlated with the subjects' disease status.

Pathogen-specific immunity will be tested serially with microbial antigens that subjects have been exposed to prior to transplant or post-transplant, when feasible. The potential assays suitable are the following:

- Cytokine Flow Cytometry (CFC)
- Luminex based multiplex cytokine detection in microculture supernatants
- ELISPOT assay to enumerate IFN-secreting antiviral cells
- Proliferation assays
- Tetramer/Pentamer assay, if applicable

## **2.4 Study Endpoints**

### **2.4.1 Primary Endpoints**

- Incidence of grade III-IV Acute GvHD within 90 days of the last cellular infusion

- Incidence of CTCAE grade 4/5 adverse events within 30 days of the last cellular infusion

#### **2.4.2 Secondary Endpoints**

- 1-year overall survival from first cellular infusion (continuous)
- 6-month overall survival from first cellular infusion (dichotomous)
- Viral load and clinical response to treatment of viral infection at 1 month, 3 months, and 6 months from first cellular infusion
- Usage of concomitant antiviral agents
- Immune reconstitution at 1 month and 3 months following first cellular infusion with a focus on adaptive T cell immunity and viral-specific responses.
- Incidence of chronic GVHD at 6 months from first cellular infusion

### **2.5 Statistical Analysis**

#### **2.5.1 Sample Size Determination and primary analysis**

With 4 years of enrollment and an additional year of follow-up, we anticipate treating ~4-7 patients/year, for a total sample size of 15-25. Patients withdrawn from the study will be replaced to maintain the sample size at a maximum of 25. For binary efficacy variables, point estimates of the rate of treatment success will be provided with 90% Wilson confidence intervals of width <40 percentage points (n=15) to <31 percentage points (n=25).

All patients will be closely monitored for infusion reactions and GVHD, with regular review of adverse event summaries by the study team. Additionally, a stopping rule is defined in section 6.4.9 to trigger additional scrutiny (including independent review).

#### **2.5.2 Efficacy Analysis**

Efficacy will be analyzed as a case series, since the patient population is heterogeneous with respect to underlying disease, HCT vs SOT vs immunocompromised patient, and infection type. Overall rates for key efficacy criteria will be reported with 90% Wilson (score) confidence intervals.

#### **2.5.3 Safety Analysis**

All reported adverse events will be coded using the NCI common toxicity criteria version 5.0. The number and percent of subjects reporting adverse events will be quantified to report the rate of serious adverse events. Summaries will include only the highest grade experienced by each subject for each adverse event. The rate of reported serious adverse events (defined in section 6.4.5) will be reported separately.

#### **2.5.4 Handling Missing Data**

Standard procedures will be used to ensure that data are as complete and accurate as possible. We will not impute values for primary or secondary endpoints, or mechanistic measures, for subjects with missing data.

#### **2.5.5 Data Management**

Data will be generated from standard of care procedures, tests, etc. and is available in the subjects' medical records.

### 3.0 HUMAN SUBJECTS and CLINICAL SITES

#### 3.1 Subject Inclusion Criteria

1. Patient, parent, or legal guardian must have given written informed consent, according to FDA guidelines. For patients  $\geq 7$  years of age who are developmentally able, assent or affirmation will be obtained, if feasible.
2. Male or female, 1 month through 65 years old, inclusive, at the time of informed consent.
3. Prior allogeneic hematopoietic stem cell transplant (bone marrow, peripheral blood stem cells, single or double cord blood), OR prior solid organ transplant (liver, kidney, lung and/or heart, intestinal, or multivisceral), OR diagnosis of primary immunodeficiency OR current/recent administration of immunosuppressive therapy for cancer or autoimmune disease.
4. Clinical status, at time of consent, amenable to tapering of steroids to less than 1 mg/kg/day prednisone (or equivalent) prior to cellular infusion.
5. Negative pregnancy test for females  $\geq 10$  years old or who have reached menarche, unless surgically sterilized.
6. Diagnosis of Adenovirus, CMV, or EBV infection, persistent despite standard therapy.
  - A. Adenovirus Infection or Disease:
    - a) Active adenovirus infection: (i.e. gastroenteritis, pneumonia, hemorrhagic cystitis, hepatitis, pancreatitis, meningitis) defined as the demonstration of adenovirus by biopsy specimen from affected site(s) (by culture or histology), or the detection of adenovirus by culture, PCR or direct fluorescent antibody stain in fluid in the presence of worsening or persistent clinical or imaging findings despite at least 14 days of appropriate antiviral therapy (i.e. cidofovir, brincidofovir, or other available pharmacological agents) **OR**
    - b) Refractory adenoviremia: defined as DNAemia  $>5000$  copies/mL or  $<1$  log decrease after at least 2 weeks of appropriate antiviral therapy (i.e. cidofovir, brincidofovir, or other available pharmacological agents) **OR**
    - c) Intolerance of or contraindication to antiviral medications.
  - B. CMV Infection or Disease:
    - a) Active CMV infection: (i.e. pneumonia, meningitis, retinitis, hepatitis, hemorrhagic cystitis, and/or gastroenteritis) defined as the demonstration of CMV by biopsy specimen from affected site(s) (by culture or histology) or the detection of CMV by culture, PCR or direct fluorescent antibody stain in fluid in the presence of worsening or persistent clinical or imaging findings despite at least 14 days of appropriate antiviral therapy (i.e. Foscarnet, ganciclovir, cidofovir, or other available pharmacological agents) **OR**
    - b) Refractory CMV viremia: defined as the continued presence of DNAemia, with  $\geq 2,000$  IU/mL or  $<1$  log decrease after at least 14 days of appropriate antiviral therapy (i.e. Foscarnet, ganciclovir, cidofovir, or other available pharmacological agents) **OR**
    - c) Intolerance of or contraindication to antiviral medications.
  - C. EBV Infection or Disease:

- a) Biopsy proven lymphoma or posttransplant lymphoproliferative disease with EBV genomes detected in tumor cells by immunocytochemistry (i.e. EBER positive) or in situ PCR, **OR**
  - b) Clinical or imaging findings consistent with EBV lymphoma and associated elevated EBV viral load in peripheral blood in a patient where biopsy is deemed too high risk, **OR**
  - c) Failure of antiviral therapy, as determined by one of the two bullets below after three weeks of anti-CD20 targeted therapy such as Rituximab.
    - i. There was an increase or less than 50% response at sites of lymphoma disease or lymphoproliferation.
    - ii. There was a rise or a fall of less than 50% in EBV viral load in peripheral blood of PTLD patients.
7. Donor Eligibility Criteria
- a) 12 years of age or older
  - b) Able to understand and consent/assent to the procedure
  - c) Hemoglobin of 11g/dL or greater
  - d) Partial (2/6 or more) HLA match to the recipient

### 3.2 Subject Exclusion Criteria

1. Received ATG or Alemtuzumab within 28 days of viral-specific T cell infusion and a lack of evidence of T cell survival, defined by <10 CD3+ T cells/uL (in unique situations, plasmapheresis may be considered).
  2. Active acute GVHD grades II-IV.
  3. Active extensive chronic GVHD.
  4. Received donor lymphocyte infusion, with the exception of a fraction of an umbilical cord blood, within 21 days of viral-specific T cell infusion. Subjects receiving a fraction of an umbilical cord blood within 21 days of the viral-specific T cell infusion will not be excluded.
  5. Active and uncontrolled relapse of malignancy (other than EBV+ post-transplant lymphoproliferative disorder or lymphoma).
  6. Anticipated initiation of new lymphotoxic therapy within 4 weeks of viral-specific T cell infusion.
  7. Patients who are pregnant or lactating.
  8. Past or current medical problems or findings from physical examination or laboratory testing that are not listed above, which, in the opinion of the investigator, may pose additional risks to participation in the study, may interfere with the participant's ability to comply with study requirements, or that may impact the quality or interpretation of the data obtained from the study.
- 1) Donor Exclusion Criteria
- a. Donor is pregnant
  - b. Donor is HIV positive
  - c. Donor is positive for hepatitis B and/or hepatitis C
  - d. Uncontrolled infection
  - e. Deemed to be a high-risk donor based on responses to donor risk questionnaire

- f. Deemed high risk due to preexisting medical condition or abnormal lab results

### 3.3 Selection of Clinical Sites

UMPC Children's Hospital of Pittsburgh, UPMC Hillman Cancer Center, UPMC Presbyterian, and UPMC Shadyside are world-renowned in healthcare. Subjects will undergo viral specific T cell infusion(s) at the locations mentioned above, based upon age and clinical discretion. Clinicians from all hospitals will follow enrolled subjects concurrently due to the integrated health care system at the University of Pittsburgh Medical Center (UPMC).

### 4.0 IRB APPROVAL AND FDA AMENDMENTS

The Investigator will obtain, from the University of Pittsburgh Institutional Review Board (IRB), prospective approval of the clinical protocol and corresponding informed consent form(s); modifications to the clinical protocol and corresponding informed consent forms, and advertisements (i.e., directed at potential research subjects) for study recruitment.

The only circumstance in which a deviation from the current IRB-approved clinical protocol/consent form(s) may be initiated in the absence of prospective IRB approval is to eliminate an apparent immediate hazard to the research subject(s). In such circumstances, the Investigator will promptly notify the University of Pittsburgh IRB of the deviation. The Investigator should also notify the sponsor of this event.

The University of Pittsburgh IRB operates in compliance with FDA regulations at 21 CFR Parts 50 and 21 CFR 56, and in conformance with applicable International Conference on Harmonization (ICH) Guidelines on Good Clinical Practice (CGP).

If the University of Pittsburgh IRB requires, as a condition of approval, substantial changes to a clinical protocol submitted under an FDA-accepted IND application, or in the event of the Investigator's decision to modify the previously accepted clinical protocol:

- for a Phase 1 clinical study: The Sponsor will submit (i.e., in advance of implementing the change) a Protocol Amendment to the IND describing any change to the Phase 1 clinical protocol that significantly affects the safety of the subjects. For changes that do not affect critical safety assessments, the revisions to the clinical protocol will be addressed in the Annual Report to the IND.
- for Phase 2 and 3 clinical studies: The Sponsor will submit (i.e., in advance of implementing the change) a Protocol Amendment to the IND describing any change to a Phase 2 or Phase 3 protocol that significantly affects the safety of subjects, the scope of the investigation, or the scientific quality of the study. Examples of Phase 2 and 3 clinical protocol changes requiring the submission of a Protocol Amendment include:
  - Any increase in drug dosage or duration of exposure of individual subjects to the investigational drug beyond that described in the current protocol, or any significant increase in the number of subjects under study.

- Any significant change in the design of the protocol (such as the addition or deletion of a control group).
- The addition of a new test or procedure that is intended to improve monitoring for, or reduce the risk of, a side effect or adverse event; or the dropping of a test intended to monitor the safety of the investigational drug.

## **5.0 RECRUITMENT AND INFORMED CONSENT PROCEDURE**

### **5.1 Recruitment Methods**

Potential subjects will be referred by their treating physicians or may be self-referred. Information to the trial, along with eligibility criteria, will be posted on [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

### **5.2 Informed Consent Procedure**

The recipient and donor consent process will provide information about the study, including procedures and risks, to a prospective participant, and will allow adequate time for review and discussion prior to his/her decision. More than one donor consent can be signed and are required prior to starting any study related activities. The principal investigator or designee listed on the FDA form 1572 will review the consent and answer questions. The prospective participant will be told that being in the trial is voluntary and that he or she may withdraw from the study at any time, for any reason. All participants (or their legally acceptable representative) will read, sign, and date a consent form before undergoing any study procedures. A copy of the signed consent form will be given to the participant and/or legally acceptable representative.

Pediatric subjects who are developmentally able to provide written assent will sign the consent document in addition to the parents or legal guardian. For children who are not determined to be developmentally able to sign the consent document, the investigator must certify that the purpose and nature of the research was explained in age appropriate language and that the child provided positive affirmation to participate. Once the child turns 18 years of age, the study team will obtain direct consent to continue with participation.

The consent form will be revised when important new safety information is available, the protocol is amended, and/or new information becomes available that may affect participation in the study.

## **6.0 POTENTIAL RISKS AND BENEFITS**

### **6.1 Potential Risks**

#### **6.1.1 Risks of Viral-Specific T Cell Infusion**

##### **6.1.1.1 Infusion reactions**

Common risks: Viral-specific T cell infusions utilizing the gamma capture methodology have been well tolerated in preliminary studies, but carry the risk of causing an allergic reaction. These symptoms may include tachycardia, hypertension, and/or rash.

Infrequent Risks: Rarely an infusion reaction could manifest as anaphylaxis. These symptoms could include: shortness of breath, wheezing, coughing, or throat tightening, swelling of the lips or tongue, trouble swallowing, hives, swelling, vomiting, diarrhea, confusion, or seizures. All

subjects will be monitored during the infusion and treated, per institutional guidelines, for any infusion reactions. The viral-specific T cell infusion may be interrupted, if deemed medically necessary.

#### **6.1.1.2 GVHD**

Infrequent risks: Although not commonly attributed to this cellular infusion, there may be a risk for GVHD. Acute GVHD may produce skin rashes, liver disease, diarrhea, and an increased risk of infection. All of these can range in severity from mild to fatal. Acute GVHD can persist and become Chronic GVHD. Chronic GVHD can also appear in people without prior acute GVHD and may also produce skin rashes, liver disease, diarrhea, scleroderma, myositis, increased risk of infection, and other symptoms. Chronic GVHD may be mild and respond to drugs that suppress the immune system, or it could be very severe.

#### **6.1.2 Blood Draw**

Common Risks: Risks of blood draw or venipuncture are typically minimal with temporary local discomfort. The amount of blood that may be drawn from adult subjects, who weigh at least 110 pounds, for research purposes will not be more than 550 mL over an eight-week period. For pediatric patients and other adults, the amount drawn may not exceed the lesser of 50 ml or 3 ml/kg in an eight-week period and collection may not occur more frequently than 2 times per week. The additional amount of blood could contribute to the development of anemia. The subject's clinical condition will be taken into consideration to determine if research blood tests can be performed.

Infrequent Risks: More serious and less common risks would include ecchymosis and, rarely, localized infection.

### **6.2 Alternative Treatments**

Subjects may continue with their standard of care treatment.

### **6.3 Potential Benefits**

This protocol may provide no direct benefit. If the viral-specific T cell infusion is successful, the subjects' infection may resolve and quality of life may improve. The results of this study could influence the future care of similar cases.

### **6.4 Data Safety Monitoring**

#### **6.4.1 Data Safety Monitoring Plan (DSMP)**

Monitoring of safety and data quality in the proposed study will be the responsibility of all personnel on the project, with primary responsibility and supervision by the Principal Investigator. The Institutional Review Board will approve the Statement of Informed Consent for the study and provide institutional oversight of data and safety issues. The study protocol will be approved prior to recruiting or obtaining consent from any participants. Moreover, the study will be reviewed every six months by the IRB committee. To ensure participant safety, once participants are enrolled in the study, study staff will immediately report all adverse and serious adverse events to one of the Investigators. The Investigator will, per standardized procedures, report them to the IRB for their review. Regarding monitoring of data

quality and protected health information, all required personnel proposed for this project will have the required human subjects and confidentiality training, which includes information about maintaining data integrity and security. Confidentiality will be guarded using established procedures such as storing data in locked cabinets within locked offices or locked data rooms, and aggregating data across participants. Only study personnel will have access to the data sets on protected servers. Oversight of all aspects of data management will occur with the Investigator.

The proposed study will use the FDA definition of adverse events (AE) and serious adverse events (SAE). Any SAE, which is unexpected and related to study intervention, will be reported immediately to the IRB and will be followed by an additional letter detailing the nature of the SAE. If a participant either withdraws from the study for any reason, clinical data may be abstracted from their medical charts for an additional 1 year post most recent viral-specific T cell infusion to assess study endpoints and overall survival. The SAE will remain open until (a) a resolution is reached (e.g., the problem has resolved or stabilized with no further change expected), (b) the SAE is determined to be clearly unrelated to the study intervention, or (c) the SAE results in death. Outcomes of SAEs will be regularly reported to the IRB and the sponsor. A summary of the SAEs that occurred during the previous year will be included in the annual progress report as well as in the annual IRB renewal.

For this study, an adverse event will include any untoward or unfavorable medical occurrence associated with the infusion of viral-specific T cells.

#### **6.4.2 Data Safety Monitoring (DSM)**

Study personnel meet at least monthly and may be comprised of the Investigator, Sub-investigators, PA-C/CRNPs, Research Coordinators, and/or BMT Coordinators. These discussions include, but not limited to, subject safety, enrollment, potential subjects, and protocol modifications (see 6.4.3). Minutes from these meetings are submitted to the UPMC Hillman Cancer Center (Hillman) DSM Committee (DSMC). An annual progress report will be submitted for review and approval.

The Data Safety and Monitoring Committee (DSMC) provides oversight of safety and compliance by regularly reviewing DSMP meeting minutes and frequency and severity of adverse events. Interim DSMC meetings are scheduled to address specific issues that require immediate attention to ensure subject safety. The DSMC also assesses relevant new information, such as published scientific reports, or other developments that may affect subject safety or ethical concerns. The DSMC review is done to determine if there are changes to the anticipated risk/benefit ratio of a study that would affect its continuation.

#### **6.4.3 Parameters to be Monitored**

The following progress will be monitored throughout the course of the research to ensure the safety of subjects as well as the integrity and confidentiality of their data:

- An evaluation of the progress of the research study, including subject recruitment and retention, and an assessment of the timeliness and quality of the data.
- A review of collected data (including adverse events, unanticipated problems, and subject withdrawals) to determine whether there is a change to the anticipated benefit-to-risk assessment of study participation and whether the study should continue as originally designed, should be changed, or should be terminated.
- An assessment of external factors or relevant information (e.g. pertinent scientific literature reports or therapeutic development, results of related studies) that may have an impact on the

- safety and study participants or the ethics of the research study.
- A review of study procedures designed to protect the privacy of the research subjects and the confidentiality of their research data.

The study site will grade the severity of adverse events experienced by the study subjects according to the criteria set forth in the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

- Grade 1 (Mild): asymptomatic or mild symptoms; clinical or diagnostic observation only; intervention not indicated.
- Grade 2 (Moderate): minimal, local or noninvasive intervention indicated; limiting age-appropriate ADL (Activities of Daily Living).
- Grade 3 (Severe): medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADLs.
- Grade 4 (Life-threatening): consequences; urgent intervention indicated.
- Grade 5 (Death): event is a direct cause of death.

Collection of AEs will begin on Day 0. All Grade 3 and greater AEs will be reported via case report forms.

#### **6.4.4 Frequency of Monitoring**

The Investigator will review subject safety data as it is generated. The Investigator and research staff will meet at least monthly, while subjects are active, otherwise, quarterly, to re-evaluate study goals, subject recruitment, data coding and retention, documentation and identification of adverse events, complaints and confidentiality of subjects. There will be an evaluation of the progress of the research study, including assessments of data quality, time lines, participant recruitment, accrual, and retention. The Investigator will also review the outcome and adverse event data to determine whether there is any change to the anticipated benefit-to-risk ratio of study participation and whether the study should continue as originally designed or should it be re-evaluated and changed.

#### **6.4.5 Reportable Adverse Events**

For this study, a serious adverse event is any untoward clinical event that is thought by either the investigator or the sponsor to be related to the study and results in any of the following outcomes:

- Death
- A life threatening adverse event
- Inpatient hospitalization or prolongation of an existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly or birth defect
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient, or subject, and may require medical, or surgical intervention to prevent one of the serious outcomes listed above

If clinically important and unexpected adverse experiences or clinically important study-related adverse

experiences occur, they will be recorded on the adverse event case report form.

#### 6.4.6 Adverse Events Reporting Timeline

Life-threatening or fatal unexpected adverse events associated with the use of the study drug or procedures must be reported to the IRB within 24 hours of discovery of the incident with subsequent follow-up submission of a detailed written report.

The FDA will be notified by telephone or facsimile transmission of a human adverse event that is fatal or life-threatening no later than 7 calendar days after receiving the respective human adverse event information, followed by the subsequent submission of a written IND Safety Report.

Serious and unexpected adverse events associated with the use of the study drug or procedures will be reported to the IRB with subsequent follow-up submission of a detailed written report in accordance with the respective policies and procedures of the IRB. Written IND Safety Reports will be submitted to the FDA as soon as possible and, in no event, later than 15 calendar days following the investigator-sponsor's receipt of the respective adverse event information.

A summary report of the findings will be prepared and submitted to the regulatory agencies.

#### 6.4.7 Attribution of Adverse Events

The relationship, or attribution, of an adverse event to the study therapy regimen or study procedure(s) will initially be determined by the site investigator and recorded on the appropriate AE/SAE Case Report Form.

Figure 3: Attribution of Adverse Events

Code	Descriptor	Relationship (to primary investigational product and/or other concurrent mandated study therapy or study procedure)
UNRELATED CATEGORY		
1	Unrelated	The adverse event is clearly not related: there is insufficient evidence to suggest a causal relationship.
RELATED CATEGORIES		
2	Possible	The adverse event has a <u>reasonable possibility</u> to be related; there is evidence to suggest a causal relationship.
3	Definite	The adverse event is clearly related.

#### 6.4.8 Withdrawal of Subjects and Stopping Criteria

##### 6.4.8.1 Participant Withdrawal Criteria

Participants may be prematurely terminated from the study for the following reasons:

- The participant elects to withdraw consent from all future study activities, including follow-up
- The subject is no longer eligible

- The participant is “lost to follow-up” (i.e., no further follow-up is possible because attempts to reestablish contact with the participant have failed)
- The participant dies
- The Investigator no longer believes participation is in the best interest of the participant

#### 6.4.8.2 Follow-up after Early Study Withdrawal

If a participant either withdraws from the study for any reason, clinical data may be abstracted from their medical charts for an additional 1 year post most recent viral-specific T cell infusion to assess study endpoints and overall survival. All subject information will be sent to a secured long-term retention facility for an indefinite period. Data collected prior to the subject’s withdrawal will be used for this trial.

#### 6.4.9 Stopping Rules

If either “primary endpoint” event happens for **any** patient

- grade 4-5 serious adverse events within 30 days of infusion, probably or definitely attributable to the cellular product infusion
- New onset of grade III-IV GVHD within 90 days of infusion, definitely attributable to the viral specific T cell infusion (competing event is absent – i.e. poor compliance with subtherapeutic drug levels of GVHD prophylaxis agent(s) and/or suspension or discontinuation of GVHD prophylaxis agent(s) due to toxicity, relapse or other cause)

it will trigger an expedited study team meeting (defined in section 6.4.2) to review all patient safety data.

“Primary endpoint” events in **multiple patients** may trigger cessation of all product administrations and mandate a comprehensive safety review, including independent medical monitors outside of the study team. This stopping rule will be triggered if 1 of the first 3, or 2 of the first 6 participants experience a Grade 3 or higher event attributable to the study intervention.

### 6.5 Risk Management Procedures

All research interventions/activities will be conducted in private patient care areas. The collection of sensitive information about subjects is limited to the amount necessary to achieve the aims of the research, so that no unneeded sensitive information is being collected.

All staff involved in this study are properly credentialed and instructed in the areas of testing, confidentiality, and safety.

The Investigator will retain the data for the entire period of this study and will retain the specified records and reports for up to two years after the marketing application is approved for the investigational treatment; or, if a marketing application is not submitted or approved for the investigational treatment, until two years after investigations under the IND have been discontinued and the FDA so notified. The Investigator may continue to use and disclose subjects’ de-identified information for this study for a minimum of seven years after final reporting or publication of the study. If the subject and/or legal representative decide to withdraw or be withdrawn from study participation,

they may request that the study data be destroyed. Subject names or other directly identifiable information will not appear on any reports, publications, or other disclosures of clinical study outcomes.

## **7.0 COSTS**

Subjects' insurance providers will be charged for all clinically indicated tests and procedures. Funds from UPMC will be utilized for non-clinically indicated tests and procedures. Subjects will not be compensated for their participation in this trial.

## **8.0 QUALIFICATIONS**

The investigators of this protocol are medical physicians within the UPMC system and have training pertinent to at least one of the following areas: hematopoietic stem cell transplantation, organ transplantation and/or infectious diseases.

## 9.0 REFERENCES

- Boeckh, M., Nichols, W. G., Papanicolaou, G., Rubin, R., Wingard, J. R., & Zaia, J. (2003). Cytomegalovirus in hematopoietic stem cell transplant recipients: Current status, known challenges, and future strategies. *Biol Blood Marrow Transplant*, 9(9), 543-558.
- Brunstein, C. G., Weisdorf, D. J., DeFor, T., Barker, J. N., Tolar, J., van Burik, J. A., & Wagner, J. E. (2006). Marked increased risk of Epstein-Barr virus-related complications with the addition of antithymocyte globulin to a nonmyeloablative conditioning prior to unrelated umbilical cord blood transplantation. *Blood*, 108(8), 2874-2880. doi:10.1182/blood-2006-03-011791
- Cohen, J. M., Cooper, N., Chakrabarti, S., Thomson, K., Samarasinghe, S., Cubitt, D., . . . Amrolia, P. J. (2007). EBV-related disease following haematopoietic stem cell transplantation with reduced intensity conditioning. *Leuk Lymphoma*, 48(2), 256-269. doi:10.1080/10428190601059837
- Curtis, R. E., Travis, L. B., Rowlings, P. A., Socie, G., Kingma, D. W., Banks, P. M., . . . Deeg, H. J. (1999). Risk of lymphoproliferative disorders after bone marrow transplantation: a multi-institutional study. *Blood*, 94(7), 2208-2216.
- Echavarria, M. (2008). Adenoviruses in immunocompromised hosts. *Clin Microbiol Rev*, 21(4), 704-715. doi:10.1128/CMR.00052-07
- Feucht, J., Opherck, K., Lang, P., Kayser, S., Hartl, L., Bethge, W., . . . Feuchtinger, T. (2015). Adoptive T-cell therapy with hexon-specific Th1 cells as a treatment of refractory adenovirus infection after HSCT. *Blood*, 125(12), 1986-1994. doi:10.1182/blood-2014-06-573725
- Feuchtinger, T., Lang, P., Hamprecht, K., Schumm, M., Greil, J., Jahn, G., . . . Einsele, H. (2004). Isolation and expansion of human adenovirus-specific CD4+ and CD8+ T cells according to IFN-gamma secretion for adjuvant immunotherapy. *Exp Hematol*, 32(3), 282-289. doi:10.1016/j.exphem.2003.12.009
- Feuchtinger, T., Lucke, J., Hamprecht, K., Richard, C., Handgretinger, R., Schumm, M., . . . Lang, P. (2005). Detection of adenovirus-specific T cells in children with adenovirus infection after allogeneic stem cell transplantation. *Br J Haematol*, 128(4), 503-509. doi:10.1111/j.1365-2141.2004.05331.x
- Feuchtinger, T., Matthes-Martin, S., Richard, C., Lion, T., Fuhrer, M., Hamprecht, K., . . . Lang, P. (2006). Safe adoptive transfer of virus-specific T-cell immunity for the treatment of systemic adenovirus infection after allogeneic stem cell transplantation. *Br J Haematol*, 134(1), 64-76. doi:10.1111/j.1365-2141.2006.06108.x
- Feuchtinger, T., Opherck, K., Bethge, W. A., Topp, M. S., Schuster, F. R., Weissinger, E. M., . . . Einsele, H. (2010). Adoptive transfer of pp65-specific T cells for the treatment of chemorefractory cytomegalovirus disease or reactivation after haploidentical and matched unrelated stem cell transplantation. *Blood*, 116(20), 4360-4367. doi:10.1182/blood-2010-01-262089
- Feuchtinger, T., Richard, C., Joachim, S., Scheible, M. H., Schumm, M., Hamprecht, K., . . . Lang, P. (2008). Clinical grade generation of hexon-specific T cells for adoptive T-cell transfer as a treatment of adenovirus infection after allogeneic stem cell transplantation. *J Immunother*, 31(2), 199-206. doi:10.1097/CJI.0b013e31815ef862
- Icheva, V., Kayser, S., Wolff, D., Tuve, S., Kyzirakos, C., Bethge, W., . . . Feuchtinger, T. (2013). Adoptive transfer of epstein-barr virus (EBV) nuclear antigen 1-specific t cells as treatment for EBV reactivation and lymphoproliferative disorders after allogeneic stem-cell transplantation. *J Clin Oncol*, 31(1), 39-48. doi:10.1200/JCO.2011.39.8495
- Kuehnle, I., Huls, M. H., Liu, Z., Semmelmann, M., Krance, R. A., Brenner, M. K., . . . Heslop, H. E. (2000). CD20 monoclonal antibody (rituximab) for therapy of Epstein-Barr virus lymphoma after hemopoietic stem-cell transplantation. *Blood*, 95(4), 1502-1505.

- Miller HK, Hanley PJ, Lang H, Lazarski CA, Chorvinsky EA, McCormack SI, . . . Keller MD5. (2018). Antiviral T Cells for Adenovirus in the Pretransplant Period: A Bridge Therapy for Severe Combined Immunodeficiency. *Biol Blood Marrow Transplant*. pii: S1083-8791(18)30252-0. doi: 10.1016/j.bbmt.2018.04.030.
- Mohty, M., Jacot, W., Faucher, C., Bay, J. O., Zandotti, C., Collet, L., . . . Blaise, D. (2003). Infectious complications following allogeneic HLA-identical sibling transplantation with antithymocyte globulin-based reduced intensity preparative regimen. *Leukemia*, 17(11), 2168-2177. doi:10.1038/sj.leu.2403105
- Myers, G. D., Bollard, C. M., Wu, M. F., Weiss, H., Rooney, C. M., Heslop, H. E., & Leen, A. M. (2007). Reconstitution of adenovirus-specific cell-mediated immunity in pediatric patients after hematopoietic stem cell transplantation. *Bone Marrow Transplant*, 39(11), 677-686. doi:10.1038/sj.bmt.1705645
- Myers, G. D., Krance, R. A., Weiss, H., Kuehnle, I., Demmler, G., Heslop, H. E., & Bollard, C. M. (2005). Adenovirus infection rates in pediatric recipients of alternate donor allogeneic bone marrow transplants receiving either antithymocyte globulin (ATG) or alemtuzumab (Campath). *Bone Marrow Transplant*, 36(11), 1001-1008. doi:10.1038/sj.bmt.1705164
- Qian, C., Campidelli, A., Wang, Y., Cai, H., Venard, V., Jeulin, H., . . . Bensoussan, D. (2017). Curative or pre-emptive adenovirus-specific T cell transfer from matched unrelated or third party haploidentical donors after HSCT, including UCB transplantations: a successful phase I/II multicenter clinical trial. *J Hematol Oncol*, 10(1), 102. doi:10.1186/s13045-017-0469-0
- Young, L. S., & Rickinson, A. B. (2004). Epstein-Barr virus: 40 years on. *Nat Rev Cancer*, 4(10), 757-768. doi:10.1038/nrc1452

## Appendix 1: Schedule of Events

Time points (Days), to be calculated from <b>FIRST</b> viral-specific T cell infusion <sup>8</sup>	Baseline	0	7	14	21	28	42	90	180	365
Visit #	-1	0	1	2	3	4	5	6	7	8
Visit Window (Days)	Footnote <sup>1</sup>		±3	±3	±3	±3	±10	±14	±30	±30
Informed consent	X									
Demographics	X									
Physical Assessment, Height, Weight	X	X	X	X	X	X	X	X	X	X
Medical History	X									
Inclusion/Exclusion	X									
Acute GvHD Assessment (see Appendix 2) <sup>2</sup>	X	X	X	X	X	X	X	X		
Chronic GvHD Assessment (see Appendix 3) <sup>2</sup>	X							X	X	
HCG Pregnancy Test, if applicable (via urine or serum)	X									
Viral PCR (adenovirus, CMV, or EBV) <sup>3</sup>	X		X	X	X	X		X	X	X
Testing for adenovirus, CMV or EBV from nasal swab or wash, BAL, urine, stool and/or other fluid/tissue, if previously positive (recommended) <sup>4</sup>	X			X		X		X	X	X
CBC w/ Differential and Platelet Count	X		X	X	X	X	X	X	X	X
Comprehensive Metabolic Panel <sup>5</sup>	X		X	X	X	X	X	X	X	X
Liver Function Tests (Alkaline phosphatase, total and direct bilirubin, ALT, AST, GGTP)	X		X	X	X	X	X	X	X	X
Immune reconstitution (Lymphocyte Subsets and DiGeorge Panel) <sup>6</sup>	X					X		X	X	X
Tacrolimus, Cyclosporine or other GVHD ppx/immunosuppression level (as clinically indicated)	To be abstracted from subjects’ medical chart at timepoints listed above.									
Fluid or biopsy of Disease Site (if clinically indicated)	PCR, culture, biopsy, etc. of disease site during study period will be abstracted from subjects’ medical chart.									
Imaging of Disease Site (if clinically indicated)	Relevant imaging performed during study period will be abstracted from subjects’ medical chart.									
STUDY INTERVENTION										
Viral-Specific T Cell Infusion		X								
DATA COLLECTION										

Time points (Days), to be calculated from <b>FIRST</b> viral-specific T cell infusion <sup>8</sup>	Baseline	0	7	14	21	28	42	90	180	365
Visit #	-1	0	1	2	3	4	5	6	7	8
Visit Window (Days)	Footnote <sup>1</sup>		±3	±3	±3	±3	±10	±14	±30	±30
Concomitant Medications		X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X
MECHANISTIC ASSAYS (optional)										
Szabolcs' Lab Mechanistic Assays (blood) <sup>7</sup>	X			X		X		X	X	
MedBio Research Specimen Bank (blood)	X			X		X		X	X	

<sup>1</sup>Baseline data to be collected within 7 days of viral-specific T cell infusion, with the exception of Informed Consent, Demographics, Medical History and Inclusion/Exclusion that may be collected outside of this window. Height to be collected at Baseline only. Baseline EBV, CMV or Adenovirus must be collected within 3 days prior to the viral-specific T cell infusion. Viral PCR on the day of infusion is encouraged.

<sup>2</sup>Acute and chronic GVHD will be assessed at all the time points noted above in HCT recipients. As clinically indicated, chronic GVHD will be assessed earlier and/or more frequently depending on the patient's timing post-transplant. All non-HCT patients will have at least one scheduled acute GVHD assessment performed by a provider trained in Hematology/Oncology and/or Bone Marrow Transplant on day +28 (±7 days), with additional assessments as clinically indicated.

<sup>3</sup>Subjects will have either Adenovirus, CMV or EBV PCR tested at the timepoints above, based upon the whichever product they received. CMV and EBV are tested in whole blood and adenovirus is tested on plasma.

<sup>4</sup>These tests are recommended, but not required. PCR testing is recommended methodology.

<sup>5</sup>Comprehensive Metabolic Panel to include: sodium, potassium, calcium, chloride, carbon dioxide, glucose, BUN, creatinine, total protein, albumin.

<sup>6</sup>Lymphocyte subsets to include enumeration of CD3, CD4, CD8, CD19, CD16/56. DiGeorge panel includes recent thymic emigrants (CD4+CD45RA+CD62L).

<sup>7</sup>Including Ex vivo characterization of T cells by flow cytometry (numerical determination of subsets) and assays for virus-specificity and/or functional activity: ELISPOT, cytokine secretion, and/or proliferation assay.

<sup>8</sup>Patients who receive more than one cellular infusion will need to be followed for an additional 90 days from the last infusion. Physical examination, acute GVHD assessment, viral PCR, laboratory evaluation including complete blood count with differential and platelets and comprehensive metabolic profile should be performed at least every 2 weeks for the first 6 weeks following antiviral T cell infusion, and 90 days after the last infusion.

## Appendix 2: Clinical Acute GvHD Assessment

Subject ID: \_\_\_\_\_

Date of Assessment: \_\_\_\_\_

### Stage Skin: (select one)

- ☐ 0: No GVHD rash
- ☐ 1: Maculopapular rash <25% of body surface area
- ☐ 2: Maculopapular rash 25-50% of body surface area
- ☐ 3: Maculopapular rash >50% of body surface area
- ☐ 4: Generalized erythroderma (>50% BSA) with bullous formation and desquamation of >5% BSA

### Lower GI: (select one)

Stage Lower GI: (select one for pediatric patient or patient <50 kg)	Stage Lower GI: (Select one for adult patient or patient >50 kg)
0: <10mL/kg/day	0: ≤ 500mL/day
1: 10-19.9 mL/kg/day	1: 500-999 mL/day
2: 20-30 mL/kg/day	2: 1000-1500 mL/day
3: >30 mL/kg/day	3: >1500 mL/day
4: Severe abdominal pain with or without ileus, or grossly bloody stool (regardless of volume) without other etiology	4: Severe abdominal pain with or without ileus, or grossly bloody stool (regardless of volume) without other etiology

### Stage Upper GI: (select one)

- ☐ 0: No protracted nausea and vomiting
- ☐ 1: Persistent nausea, vomiting or anorexia with a positive upper GI biopsy

### Stage Liver (Bilirubin): (select one)

- ☐ 0: <2 mg/dL
- ☐ 1: 2.0-3.0 mg/dL
- ☐ 2: 3.1 – 6.0 mg/dL
- ☐ 3: 6.1- 15.0 mg/dL
- ☐ 4: >15 mg/dL

### Overall grade: (select one)

- ☐ 0: No stage 1-4 any organ
- ☐ I: Stage 1-2 skin and no liver or GI involvement
- ☐ II: Stage 3 skin, or stage 1 liver or GI involvement
- ☐ III: Stage 0-3 skin with stage 2-3 liver or stage 2-4 GI
- ☐ IV: Stage 4 skin or liver

\_\_\_\_\_  
Printed Name of Provider Assessing Subject

\_\_\_\_\_  
Signature of Provider Assessing Subject

\_\_\_\_\_  
Date

### Appendix 3: Clinical Chronic GvHD Assessment

Subject ID: \_\_\_\_\_

Date of Assessment: \_\_\_\_\_

PERFORMANCE SCORE:

Which scoring method used? (Circle one)

Karnofsky  
Lansky  
ECOG

SCORE 0	SCORE 1	SCORE 2	SCORE 3
Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	Symptomatic, ambulatory, capable of self-care, >50% of waking hours out of bed (ECOG 2, KPS or LPS 60-70%)	Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LP <60%)

**SKIN:** Skin scoring should use both percentage of BSA involved by disease signs and the cutaneous feature scales. When a discrepancy exists between the percentage of total body surface (BSA) score and the skin feature score, OR if superficial sclerotic features are present (Score 2), but there is impaired mobility or ulceration (Score 3), the higher level should be used for the final skin scoring.

SCORE % BSA:

SCORE 0	SCORE 1	SCORE 2	SCORE 3
No BSA involved	1-18% BSA	19-50% BSA	>50% BSA

GVHD features to be scored by BSA:

Check all that apply:

- ☐ Maculopapular rash/erythema
- ☐ Lichen planus-like features
- ☐ Sclerotic features
- ☐ Papulosquamous lesions or ichthyosis
- ☐ Keratosis pilaris-like GVHD

SKIN FEATURES SCORE:

SCORE 0	SCORE 1	SCORE 2	SCORE 3
No sclerotic features		Superficial sclerotic features "not hidebound" (able to pinch)	Deep sclerotic features "Hidebound" (unable to pinch) Impaired mobility Ulcerations

**Other skin GVHD features (NOT scored by BSA)**

Check all that apply:

- ☐ Hyperpigmentation
- ☐ Hypopigmentation
- ☐ Poikiloderma
- ☐ Severe or generalized pruritus
- ☐ Hair Involvement
- ☐ Nail Involvement
- ☐ Abnormally present but explained entirely by non-GVHD documented cause (specify): \_\_\_\_\_

MOUTH:

Lichen planus-like features present? ☐ Yes ☐ No

SCORE 0	SCORE 1	SCORE 2	SCORE 3
No symptoms	Mild symptoms <b>with</b> disease signs but not limiting oral intake significantly	Moderate symptoms <b>with</b> disease signs with partial limitation of oral intake	Severe symptoms with disease signs on examination <b>with</b> major limitations of oral intake

Abnormality present but explained entirely by non-GVHD documented cause (specify): \_\_\_\_\_

EYES:

Keratoconjunctivitis sicca (KCS) confirmed by ophthalmologist: ☐ Yes ☐ No ☐ Not Examined

SCORE 0	SCORE 1	SCORE 2	SCORE 3
No symptoms	Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops $\leq 3$ x per day)	Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops $> 3$ x per day or punctal plugs), <b>without</b> new vision impairments due to KCS	Severe dry eye symptoms significantly affecting ADL (special eyewear to relieve pain) <b>or</b> unable to work because of ocular symptoms <b>or</b> loss of vision due to KCS

Abnormality present but explained entirely by non-GVHD documented cause (specify): \_\_\_\_\_

GI TRACT:

Check all that apply:

- ☐ Esophageal web/proximal stricture or ring
- ☐ Dysphagia
- ☐ Anorexia
- ☐ Nausea
- ☐ Vomiting
- ☐ Diarrhea
- ☐ Weight loss  $\geq 5\%$  within 3 months
- ☐ Failure to thrive
- ☐ Abnormally present but explained entirely by non-GVHD documented cause (specify): \_\_\_\_\_

SCORE 0	SCORE 1	SCORE 2	SCORE 3
No symptoms	Symptoms without significant weight loss* ( $< 5\%$ )	Symptoms associated with mild to moderate weight loss* (5-15%) <b>OR</b> moderate diarrhea without significant interference with daily living	Symptoms associated with significant weight loss* ( $> 15\%$ ) requires nutritional supplement for most caloric needs <b>OR</b> esophageal dilation <b>OR</b> severe diarrhea with significant interference with daily living

\*Weight loss in last 3 months

LIVER:

SCORE 0	SCORE 1	SCORE 2	SCORE 3
Normal total bilirubin and ALP or AP <3xULN	Normal total bilirubin with ALT $\geq$ 3 to 5x ULN or AP $\geq$ 3x ULN	Elevated total bilirubin but $\leq$ 3 mg/dL or ALT >5 ULN	Elevated total bilirubin >3 mg/dL

ALT- alanine aminotransferase, AP= alkaline phosphatase

Abnormality present but explained entirely by non-GVHD documented cause (specify): \_\_\_\_\_

**LUNGS:** Lung scoring should be performed using both the symptoms and FEV1 score whenever possible. FEV1 should be used in the final lung scoring where there is discrepancy between symptoms and FEV1 scores.

SYMPTOM SCORE:

SCORE 0	SCORE 1	SCORE 2	SCORE 3
No symptoms	Mild symptoms (shortness of breath after climbing one flight of steps)	Moderate symptoms (shortness of breath after walking on flat ground)	Severe symptoms (shortness of breath at rest; requiring O <sub>2</sub> )

FEV1 SCORE:

SCORE 0	SCORE 1	SCORE 2	SCORE 3
FEV1 $\geq$ 80%	FEV1 60-79%	EV1 40-59%	FEV1 $\leq$ 39%

Pulmonary Function tests performed: ☐ Yes ☐ No

Abnormality present but explained entirely by non-GVHD documented cause (specify): \_\_\_\_\_

JOINTS AND FASCIA:

SCORE 0	SCORE 1	SCORE 2	SCORE 3
No symptoms	Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) <b>AND</b> not affecting ADL	Tightness of arms or legs <b>OR</b> joint contractures, erythema thought due to fasciitis, moderate decrease ROM <b>AND</b> mild to moderate limitation of ADL	Contractures <b>WITH</b> significant decrease of ROM <b>AND</b> significant limitation of ADL (unable to tie shoes, button shirts, dress self etc)

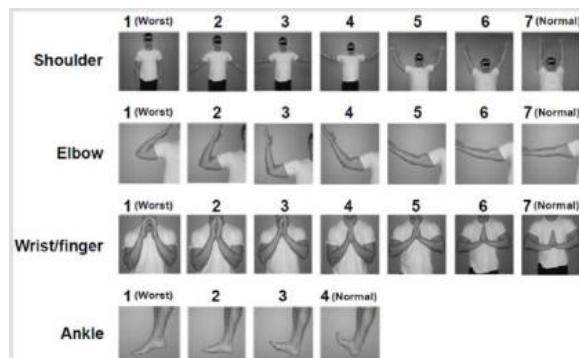
**P-ROM Score:**

Shoulder (1-7): \_\_\_\_\_

Elbow (1-7): \_\_\_\_\_

Wrist/finger (1-7): \_\_\_\_\_

Ankle (1-4): \_\_\_\_\_



Abnormality present but explained entirely by non-

GVHD documented cause (specify): \_\_\_\_\_

**GENITAL TRACT:**

☐ Not Examined

Currently Sexually active:

☐ Yes

☐ No

SCORE 0	SCORE 1	SCORE 2	SCORE 3
No signs	Mild signs and females with or without discomfort on exam	Moderate signs and may have symptoms with discomfort on exam	Severe signs with or without symptoms

Abnormality present but explained entirely by non-GVHD documented cause (specify): \_\_\_\_\_

**Other indicators, clinical features or complications related to GVHD (check all that apply and assign a score to severity (0-3) based on functional impact where applicable none-0, mild-1, moderate-2, severe-3)**

☐ Ascites (serositis) \_\_\_\_\_

☐ Pericardial effusion \_\_\_\_\_

☐ Pleural Effusion(s) \_\_\_\_\_

☐ Nephrotic syndrome \_\_\_\_\_

☐ Myasthenia Gravis \_\_\_\_\_

☐ Peripheral Neuropathy \_\_\_\_\_

☐ Polymyositis \_\_\_\_\_

☐ Weight loss >5% without GI symptoms \_\_\_\_\_

☐ Eosinophilia >500/ $\mu$ L \_\_\_\_\_

☐ Platelets <100,00/ $\mu$ L \_\_\_\_\_

☐ Others (specify): \_\_\_\_\_

**OVERALL GVHD SEVERITY (see global scaling criteria below#)**

☐ No GVHD

☐ Mild GVHD

☐ Moderate GVHD

☐ Severe GVHD

\_\_\_\_\_  
Printed name of Provider Assessing Subject

\_\_\_\_\_  
Signature of Provider Assessing Subject

\_\_\_\_\_  
Date

## #NIH Global Severity of chronic GVHD

### Mild chronic GVHD

1 or 2 Organs involved with no more than score 1 *plus*

Lung score 0

### Moderate chronic GVHD

3 or More organs involved with no more than score 1

OR

At least 1 organ (not lung) with a score of 2

OR

Lung score 1

### Severe chronic GVHD

At least 1 organ with a score of 3

OR

Lung score of 2 or 3

### Key points:

- In skin: higher of the 2 scores to be used for calculating global severity.
- In lung: FEV1 is used instead of clinical score for calculating global severity.
- If the entire abnormality in an organ is noted to be unequivocally explained by a non-GVHD documented cause, that organ is not included for calculation of the global severity.
- If the abnormality in an organ is attributed to multifactorial causes (GVHD plus other causes) the scored organ will be used for calculation of the global severity regardless of the contributing causes (no downgrading of organ severity score).

Reference: Jagasia MH, Hildegard HT, Arora M, Williams KM, Wolff D, Cowen EW...Flowers MED (2015). National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group Report. Biol Blood Marrow Transplant, 21 (3), 389-401. DOI: 10.1016/j.bbmt.2014.12.001