THIS PROTOCOL AND ALL OF THE INFORMATION RELATING TO IT IS CONFIDENTIAL AND PROPRIETARY PROPERTY OF MERCK SHARP & DOHME Ltd.

SPONSOR:
Merck Sharp & Dohme Ltd.
Hertford Road
Hoddesdon
Hertfordshire
EN11 9BU

TITLE: Analysis of the Burden of Cytomegalovirus Infection and Disease in Hematopoietic Stem Cell Transplant Recipients

INVESTIGATOR:
Dr Eduardo Olavarria
BMT Program Director
Consultant Haematologist
Hammersmith Hospital
Imperial College Healthcare NHS Trust
Du Cane Road
London W12 0HS

Table of Contents

Sponsor Contact Information

Jude Robinson
Research Manager
Medical Affairs
Hertford Road,
Hoddesdon,
HERTS, EN11 9BU
UK
01992 45 5216

judith.robinson@merck.com

Jonathan Schelfhout
Dir, Outcomes Research
MAILSTOP UG2MW05
351 North Sumneytown Pike
P.O. Box 1000
North Wales
PA, USA
Mobile: 267-406-1813
Phone: 267-305-0635

jonathan.schelfhout@merck.com

PROTOCOL SUMMARY

Title	Analysis of the Burden of Cytomegalovirus Infection and Disease in Hematopoietic Stem Cell Transplant Recipients
Vendor/Collaborator	N/A
Rationale	Currently available antiviral agents for CMV management are associated with significant toxicities including myelosuppression (ganciclovir, valganciclovir, and cidofovir) and nephrotoxicity (foscarnet and cidofovir). Hence, better devised preventive strategies (i.e. inclusion of antiviral agents with non-significant toxicities when available) can have a significant financial impact on institution's performance with clinically focused metrics.
Primary Objective(s)	To evaluate the clinical and economic consequences of CMV infection, through analysis of the incidence of CMV infection and disease in patients with haematological malignancies following allogeneic stem cell transplantation at the BMT Unit of the Hammersmith Hospital.
Study Design	In this study, we will explore the incidence of CMV reactivation and disease in patients undergoing allogeneic stem cell transplantation. We will analyze the dynamics of PCR values and the response to the different treatment options. Finally, we will evaluate the health economics associated with CMV infection in this setting.
Study Population	We will interrogate a database of approximately 350 HSCT patients, that have received care at Hammersmith between early 2004 and 2015/2016 (minimum follow-up period of one year). This database contains robust data on the recurrence of CMV, as well as complications potentially associated with CMV and the healthcare resource utilization needed to treat CMV related complications.
Study Duration	Data collected on patients that have received allogeneic stem cell transplantation at the BMT Unit of the Hammersmith Hospital between early 2004 and 2015/2016 (minimum follow-up period of one year).
Exposure and Outcome	Data on Clinical and Economic burden of CMV Infection and Disease in Hematopoietic Cell Transplant Recipients.
Statistical Methods	The database will be closed for analysis in December 2017. Demographics will be compared between identified groups (i.e. reactivated vs non-reactivated, etc.) using the Chi-square test or Fisher exact test for categorical variables and Mann-Whitney U-test for continuous variables. Probabilities of EFS and OS will be estimated from the time of transplantation using Kaplan-Meier estimates. The occurrence of engraftment, acute and chronic GVHD, NRM, and REL will be calculated using cumulative incidence estimates taking into consideration the competing events, in keeping with EBMT statistical guidelines. Factors with impact in univariate analyses, will be analyzed in multivariate analyses for their association with NRM, REL, EFS, and OS by Cox regression multivariate analyses, using a backward-stepping procedure.
Sample Size and Power Calculations	In this study, we will utilize a database of approximately 350 HSCT patients who received care at Hammersmith between 2004 and 2015/2016.
Limitations	The results of the study must be interpreted in consideration of the known limitations of chart review studies.

1. Background and Rationale

1.1 Background

CMV in allogeneic haematopoietic stem cell transplant (HSCT) recipients

Cytomegalovirus (CMV) is one of the major infectious causes of morbidity following HSCT.[1-5] The CMV genome encodes approximately 200 proteins[6] and is able to infect several cell types, such as endothelial cells, epithelial cells (including retinal cells), smooth muscle cells, fibroblasts, leukocytes, and dendritic cells.[2] As a result, CMV can affect almost every organ system, with frequent recurrences, negatively impacting on graft and patient survival after HSCT.[7] All allogeneic HCST recipients are at risk for CMV infection progressing to multi-organ disease, including pneumonia, hepatitis, gastroenteritis, retinitis, and encephalitis.[3]

1.2 Rationale

Regardless of the advances in the treatment of CMV disease, CMV infection can lead to end-organ disease constituting a major cause of morbidity and mortality for transplant recipients.[1] In the first 100 days after allogeneic HSCT, current strategies to manage CMV infection by early detection of CMV reactivation and the use of preemptive antiviral therapy decreased the incidence of CMV end-organ disease to <10 %[1,4,5] but this strategy is associated with numerous morbidities, and sometimes mortality with subsequent high economic burden secondary to hospitalization and management of antiviral toxicities. Currently available antiviral agents for CMV management are associated with significant toxicities including myelosuppression (ganciclovir, valganciclovir and cidofovir) and nephrotoxicity (foscarnet and cidofovir). Hence, better devised preventive strategies (i.e. inclusion of antiviral agents with non-significant toxicities when available) can have a significant financial impact on institution's performance with clinically focused metrics.[6]

2. Objectives and Hypotheses

2.1 Primary Objective & Hypothesis

- To determine the cumulative incidence of CMV infection and CMV-associated disease in CMV seropositive patients with haematological malignancies, following allogeneic stem cell transplantation at the BMT Unit of the Hammersmith Hospital

2.2 Secondary Objectives

- To estimate risks for infection and disease, including associations with key patient demographics and treatment (i.e. type of transplant, treatment post-transplant, CMV-specific treatment) related characteristics
- To estimate morbidity and mortality associated with CMV reactivation and serious outcomes (GVHD, graft loss, other serious infections and death)
- To estimate cumulative patient morbidity associated with specific CMV treatments and serious outcomes (other bacterial, fungal and/or viral infections, drug-associated toxicities and death)
- To evaluate the dynamics of PCR values and their correlation with the response to the different CMV-specific treatments
- To estimate healthcare resource utilization within unique cohorts, by estimating length of inpatient stay and recurrent hospitalization rates (incl. ICU utilisation)

3. Methodology

3.1 Summary of Study Design

In this single-centre, retrospective, observational study, we will explore the incidence of CMV reactivation and disease in patients undergoing allogeneic stem cell transplantation. We will analyze the dynamics of PCR values and the response to the different treatment options. Finally, we will evaluate the health economics associated with CMV infection in this setting.

3.2 Study Population

In this study, we will utilize a large database of HSCT patients who received care at Hammersmith between early 2004 and 2015/2016 (allowing for a minimum follow-up period of one year). This database contains robust data on CMV recurrence rates, as well as complications, potentially associated with CMV, and the healthcare resource utilization needed to treat CMV-related complications.

3.3 Inclusion Criteria

All patients (over 18 years of age), which have received allogeneic stem cell transplantation at the BMT Unit of the Hammersmith Hospital between early 2004 and 2015/2016 (allowing for a minimum follow-up period of one year post-transplantation). Allogeneic HSCT patients (recipients and/or donors) must be seropositive for CMV.

3.4 Exclusion Criteria

Recipient-patients which have tested seronegative for CMV, receiving stem cells from a CMV seronegative donor. Autografts are not within study scope.

4 Variables and Epidemiological Measurements

Primary Endpoint:

- To determine the cumulative incidence of CMV infection and CMV-associated disease in CMV seropositive patients with haematological malignancies, following allogeneic stem cell transplantation at the BMT Unit of the Hammersmith Hospital

Secondary Endpoints:

- Analyse the risk factors for CMV infection and disease in CMV seropositive patients post allogeneic HSCT (approximately 200 recipients)

- Report on transplant related mortality and CMV infection-related mortality
- Analyse the incidence of GVHD, graft failure, other serious infections (incl. bacterial, viral other than CMV and fungal)
- Overall and event-free survival rates
- Dynamics of CMV PCR values in relation to different CMV-specific treatment
- Calculation of health economics including length of inpatient stay and recurrent hospitalization rates (incl. ICU readmissions)

4.2 Outcomes

Data fields and variables:

PATIENT CHARACTERISTICS
Hospital number
Sex
Date of birth (age at transplant)
CMV serostatus
Disease type
Disease status at transplant
DONOR CHARACTERISTICS
Relationship: sibling, unrelated, haplo
If unrelated: Number of mismatches and type of mismatch: class I, class II
Sex
Date of birth (age at transplant)
CMV serostatus
TRANSPLANT CHARACTERISTICS
Stem cell source: BM, PB
Conditioning: RIC vs MAC
T cell depletion: no, Campath, ATG, CD34 selection
GVHD Prophylaxis: CsA + MTX, Sirolimus, PTHD-Cyclo, Other
Date of Transplant
Date of neutrophil engraftment (days until engraftment)
Date of platelet engraftment (days until engraftment)

TRANSPLANT OUTCOMES

Overall Survival

Disease Free Survival

Even-free Survival

Relapse Rate

Non-relapse Mortality

DLI yes/no

Date of DLI

FIRST CMV REACTIVATION

Date of reactivation (days until first CMV reactivation)

Copies (PCR) of CMV on date of reactivation

Type of first line treatment: Ganciclovir, Valganciclovir, Foscarnet, Cidofovir

Date starting first line treatment

Date finishing first line treatment (duration of first line treatment)

Lymphocyte count at CMV reactivation

Second line treatment: yes/no

Reason for second line treatment: failure/toxicity

Copies (PCR) of CMV on date of starting second line treatment

Type of treatment: Ganciclovir, Valganciclovir, Foscarnet, Cidofovir

Date starting second line treatment

Date finishing second line treatment (duration of second line treatment)

Third line treatment: yes/no

Reason for third line treatment: failure/toxicity

Copies (PCR) of CMV on date of starting third line treatment

Type of treatment: Ganciclovir, Valganciclovir, Foscarnet, Cidofovir

Date starting third line treatment

Date finishing third line treatment (duration of third line treatment)

FACTORS INFLUENCING FIRST CMV REACTIVATION

GVHD prior to CMV reactivation

If yes: Type

Grade

Steroids prior to CMV reactivation

Fungal disease prior to reactivation

GCSF prior to reactivation

FIRST CMV REACTIVATION OUTCOME

Complete response: yes/no

Date when complete response

Interval CMV reactivation to complete response

CMV disease Yes/no

If yes: Pneumonia, gastrointestinal, retinal

Date of documented CMV disease

Tissue specimen: BAL, gastric biopsy…

RELAPSE OF CMV REACTIVATION

Relapse of CMV reactivation: Yes/no

Date of relapse of CMV reactivation

Copies (PCR) of CMV on date of relapse of CMV reactivation

Type of treatment: Ganciclovir, Valganciclovir, Foscarnet, Cidofovir

Date when first treatment for relapse was started

Date when first treatment for relapse was finished

Lymphocytes at relapse of CMV reactivation

FACTORS INFLUENCING RELAPSE OF CMV REACTIVATION

GVHD prior to relapse of CMV reactivation

If yes: Type

Grade

Steroids prior to relapse of CMV reactivation

Fungal disease prior to relapse of CMV reactivation

GCSF prior to relapse of CMV reactivation

CMV REACTIVATION RELAPSE OUTCOME

Complete response yes/no

Date when complete response

Interval CMV reactivation to complete response

CMV disease Yes/no

If yes: Pneumonia, gastrointestinal, retinal

Date of documented CMV disease

Tissue specimen: BAL, gastric biopsy…

HEALTH ECONOMICS

Transplant admission:

Date of first readmission

Reason for readmission (CMV-related: YES/NO)

Date of first discharge (length of admission)

Days on antibiotics

Days on antifungals

Days on (non-CMV) antivirals

Acute renal injury: yes, no (creatinine level)

ICU admission: yes, no

Days in ICU

Subsequent admission:

Date of subsequent readmission

Reason for readmission (CMV-related: YES/NO)

Date of discharge (length of subsequent admission)

Days on antibiotics

Days on antifungals

Days on (non-CMV) antivirals

Acute renal injury: yes, no (creatinine level)

ICU admission: yes, no

Days in ICU

4.3 Covariates

5 STUDY PROCEDURES

5.1 General Informed Consent

The study is retrospective and will consist of the database that is currently under development in the Haematology Department at the Hammersmith Hospital. A submission to the Institutional Review Board (IRB) has been approved for this dataset, and The Clinical Trials Office of the Haematology Department at the Hammersmith Hospital will address any further IRB.

6 Safety Reporting and Related Procedures

Adverse Event Reporting Language for Non-Interventional Study Protocols

Introduction

This is a non-interventional study based on secondary use of data collected from healthcare professionals or consumers for other purposes. No administration of any therapeutic or prophylactic agent is required in this protocol, and there are no procedures required as part of this protocol.

6.1 Adverse Event Reporting

6.1.1 INVESTIGATOR RESPONSIBILITY:

Although adverse events are not actively solicited in this study, there are certain circumstances in which individual adverse events will be reported. For example, during review of medical records or physician notes (paper or electronic), to collect data as required by the protocol, if a notation of a serious adverse reaction (SAR), including death, or a non-serious adverse reaction (NSAR) to any MSD product is identified, the event must be reported according to Table 1.

Similarly, pre-specified Health Outcomes of Interest (HOIs) that meet criteria for SAR/NSAR, special situations, and any spontaneously reported AEs must be reported according to Table 1.

Table 1: AE Reporting Timeframes and Process for Investigators and Vendors

EVENT TYPE	INVESTIGATOR TIMEFRAMES	
	Investigator to MSD	
SAR Pre-specified HOI that meets criteria of SAR Serious Special Situation, regardless of causality	24 hours from receipt	
NSAR Pre-specified HOI that meets criteria of NSAR Non-serious Special Situation, regardless of causality	10 CD from receipt	
Spontaneously reported adverse events for MSD products-submit using above timeframes		
If the investigator elects to submit AEs for **non-MSD products**, they should be reported to the market authorization holder (MAH) for that product or to the health authority according to the institution's policy or local laws and regulations.		
Follow-up to any event-submit using above timeframes		
BD-Business Day; CD-Calendar Day		

Submitting AE Reports to MSD Global Safety: All AEs must be submitted via Fax to MSD UK Pharmacovigilance Department at 0032 2402 5990, in English using an AE form for reporting to worldwide regulatory agencies as appropriate.

6.2 DEFINITIONS

6.2.1 Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered sponsor's product and which does not necessarily have to have a causal relationship with this product. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of the product, whether or not considered related to the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the product, is also an adverse event.

6.2.2 Adverse Reaction (AR); also referred to as Adverse Drug Reaction (ADR)

An AE which has a causal relationship with the product, that is, a causal relationship between the product and the adverse event is at least a reasonable possibility.

6.2.3 Serious Adverse Event (SAE)/Serious Adverse Reaction (SAR)

An adverse event or adverse reaction that results in death, is life threatening, results in persistent or significant disability/incapacity, requires inpatient hospitalization,

prolongation of existing inpatient hospitalization, is a congenital anomaly/birth defect, or is another important medical event. Other important medical events that may not result in death, may not be life-threatening, or may not require hospitalization may be considered an SAE/SAR 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 other outcomes listed previously. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home and blood dyscrasias or convulsions that do not result in inpatient hospitalization.

6.2.4 Non-serious Adverse Reaction (NSAR)

An adverse reaction that does not meet any of the serious criteria in 6.2.3.

6.2.5 Special Situations

The following special situations are considered important safety information and must be reported, regardless of seriousness or causality, if the investigator becomes aware of them:

- Overdose
- Exposure to product during pregnancy or lactation
- Lack of therapeutic effect
- Off-label use, medication error, misuse, abuse, or occupational exposure
- Suspected transmission via a medicinal product of an infectious agent

6.2.6 Health Outcome of Interest (HOI)

Health Outcomes of Interest (HOIs) are pre-specified clinical events or outcomes that are collected according to the protocol. HOIs may be represented as diagnosis, treatment or procedures. Examples of HOIs include syncope or hypoglycaemia collected as study endpoints. HOIs must be assessed as part of AE collection and may meet criteria for AE reporting. Specifically, the investigator must assess each HOI for serious criteria and causality. If the HOI meets criteria specified in the protocol for AE reporting, then it must be reported as such.

6.2.7 Sponsor's Product

Sponsor's product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator product) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

6.2.8 Causality Assessment

A causality assessment is the determination of whether or not there is at least a reasonable possibility that a product caused the adverse event. Causality must be recorded on the AE form for each reported event in relationship to a Sponsor's product.

Secondary Data Collection

Only AEs with an explicit and definitive notation (by a healthcare provider) of a causal relationship with a product in the medical records or other secondary data being reviewed should be reported as NSAR/SARs. During review of secondary data, causality should never be assigned retrospectively.

7 Statistical Analysis Plan

7.1 Statistical Methods

The database will be closed for analysis in December 2017. Demographics will be compared between groups using the Chi-square test or Fisher exact test for categorical variables and Mann-Whitney U-test for continuous variables. Probabilities of EFS and OS will be estimated from the time of transplantation using Kaplan-Meier estimates. The occurrence of engraftment, acute and chronic GVHD, NRM, and REL will be calculated using cumulative incidence estimates taking into consideration the competing events, in keeping with EBMT statistical guidelines. Factors with impact in univariate analyses, will be analyzed in multivariate analyses for their association with NRM, REL, EFS, and OS by Cox regression multivariate analyses, using a backward-stepping procedure.

7.3 Sample Size

In this study, we will utilize a database of approximately 350 HSCT patients who received care at Hammersmith between 2004 and 2015/2016.

8 ADMINISTRATIVE AND REGULATORY DETAILS

8.1 Confidentiality

8.1.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the Institutional Review Board, Ethics Review Committee or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

8.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), Institutional Review Board/Independent Ethics Committee (IRB/IEC), or Regulatory Agency representatives may consult and/or copy study documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If study documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all subject data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations.

8.1.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and study site personnel, may be used and disclosed for study management purposes, as part of a regulatory submissions, and as required by law. This information may include:

- name, address, telephone number and e-mail address;
- hospital or clinic address and telephone number;
- curriculum vitae or other summary of qualifications and credentials; and
- other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other

countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory agencies or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

If this is a multicenter study, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

8.2 Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor or through a secure password-protected electronic portal provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

8.3 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Pharmacoepidemiology Practice and all applicable federal, state and local laws, rules and regulations relating to the conduct of the study.

The investigator also agrees to allow monitoring, audits, Institutional Review Board/Independent Ethics Committee review and regulatory agency inspection of study-related documents and procedures and provide for direct access to all study-related source data and documents.

The investigator agrees not to seek reimbursement from subjects, their insurance providers or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The Investigator shall prepare and maintain complete and accurate study documentation in compliance with Good Pharmacoepidemiology Practice, standards and applicable

federal, state and local laws, rules and regulations; and, for each subject participating in the study, provide all data, and, upon completion or termination of the study, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the investigator's site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory agencies. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the study documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the study in accordance with their institution's records retention schedule which is compliant with all applicable regional and national laws and regulatory requirements. If an institution does not have a records retention schedule to manage its records long-term, the investigator must maintain all documentation and records relating to the conduct of the study for 5 years after final report or first publication of study results, whichever comes later, per GPP guidelines. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. All study documents shall be made available if required by relevant regulatory authorities. The investigator must consult with the Sponsor prior to discarding study and/or subject files.

The investigator will promptly inform the Sponsor of any regulatory agency inspection conducted for this study.

Persons debarred from conducting or working on studies by any court or regulatory agency will not be allowed to conduct or work on this Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor will promptly notify that site's IRB/IEC.

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center study (including multinational). When more than one study site is open in an EU country, MSD, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different sites in that Member State, according to national regulations. For a single-center study, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review

the study report that summarizes the study results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the study in the study's final report. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the CI during the anticipated review process, thorough understanding of study methods, appropriate enrollment of subject cohort, timely achievement of study milestones). The Protocol CI must be a participating study investigator.

8.5 Quality Management System

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that studies are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Pharmacoepidemiology Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the study.

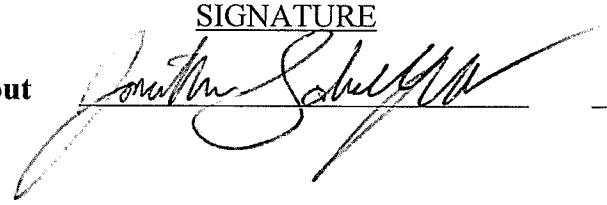
8.6 Data Management

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

For an outsourced study the institutional policies of the vendor should be followed for development of data management plans. However, the vendor should ensure compliance with Good Pharmacoepidemiology Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the study.

12 SIGNATURES

Sponsor's Representative

TYPED NAME	SIGNATURE	DATE
Jonathan Schelfhout		10/19/2017
Investigator		

I agree to conduct this study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol); deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment. I agree to conduct the study in accordance with generally accepted standards of Good Pharmacoepidemiology Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse experiences as defined in Section 6 – Safety Reporting and Related Procedures. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the study is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure, or access by third parties.

TYPED NAME	SIGNATURE	DATE
Eduardo Olavarria	_____	_____

9 Publications

This study is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript.

10 References

1. Boeckh M, Leisenring W, Riddell SR, Bowden RA, Huang ML, Myerson D, Stevens-Ayers T, Flowers ME, Cunningham T, Corey L. Late cytomegalovirus disease and mortality in recipients of allogeneic hematopoietic stem cell transplants: Importance of viral load and T-cell immunity. Blood 2003; 101:407–414.

2. Ljungman P, Griffths P, Paya C. Definitions of Cytomegalovirus Infection and Disease in Transplant Recipients. Clin Inf Dis 2002; 34:1094-7.

3. Boeckh, M. and P. Ljungman. How we treat cytomegalovirus in hematopoietic cell transplant recipients. Blood 2009; 113(23): 5711-19.

4. Freeman RB Jr. The "indirect" effects of cytomegalovirus infection. Am J Transplant 2009; 9:2453–2458.

5. Green ML, Leisenring W, Xie H, Mast TC, Cui Y, Sandmaier BM, Sorror ML, Goyal S, Özkök S, Yi J, Sahoo F, Kimball LE, Jerome KR, Marks MA, Boeckh M. Cytomegalovirus viral load and mortality after haemopoietic stem cell transplantation in the era of pre-emptive therapy: a retrospective cohort study. Lancet Haematol 2016; 3(3):e119-27.

6. Boeckh, M. and A. P. Geballe. Cytomegalovirus: pathogen, paradigm, and puzzle. Journal of Clinical Investigation 2011; 121(5):1673-80.

7. Ljungman P, Brand R, Hoek de la Camara R, Cordonnier C, Einsele H, Styczynski J, Ward KN, Cesaro S; Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation. Donor cytomegalovirus status influences the outcome of allogeneic stem cell transplant: A study by the European group for blood and marrow transplantation. Clin Infect Dis 2014; 59:473–481.

11 Appendices