Data Management Plan

Protocol Title:	**EVALUATION OF THE PHARMACOKINETICS AND PHARMACODYNAMICS OF GANCICLOVIR IN PREMATURE INFANTS RECEIVING TREATMENT FOR CYTOMEGALOVIRUS INFECTION, DMID 11-0067, Version 1.0 25 September 2012**
Protocol No./Trial Registry No.:	DMID 11-0067
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1. Introduction

The purpose of the Data Management Plan (DMP) is to define and provide instructions regarding the conduct of data management processes for protocol DMID 11-0067. The DMP will identify:

- The work to be performed
- Responsible individual/groups
- Applicable SOPs and guidelines
- Required documentation to be produced

Definition of terms and abbreviations to be used in this plan:

AE = Adverse Event
COTR = Contract Officer Technical Representative
CRF = Case Report Form
CSC = Clinical Studies Coordinator
CU = Central Unit
DCC = Data Coordinating Center
DM = Data Management Director
DMID = Division of Microbiology and Infectious Diseases
DMP = Data Management Plan
eCRF = electronic Case Report Form
eDEMS = Electronic Data Entry Management System
ISM = Independent Safety Monitor
PD = Program Director
PI = Principal Investigator
PK = Pharmacokinetic
SDW = Source Document Worksheets
TBD = To Be Determined
TBN = To Be Named
UAB = University of Alabama at Birmingham

2. Responsibilities and Scope of Work

Team Member	Role	Contact Details
Data Coordinating Center (DCC)		
Gary Cutter, PhD	Director	cutterg@uab.edu
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Division of Microbiology and Infectious Diseases (DMID)		
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Refer to ***Appendix A*** for allocation of data management responsibilities.

3. Data Analysis Plan

The Data Analysis Plan (***Appendix B***) was prepared by the DCC in conjunction with the CU leadership and approved by DMID prior to implementation of the study. Primary and secondary outcomes are addressed and the CRFs (annotated and with variable rules) containing each of the key outcome variables will be provided on request.

4. CRF Design and Function

The CRF development, design and function will be achieved with collaboration between the CU and DCC. The CU staff (PD and CSC) and the DCC are responsible for developing the User Requirement Specifications (URS) (***Appendix C***); this document is submitted to the DCC Systems IT Director and developers.

1. Who is responsible for design?

The CU staff (PD and CSC), in conjunction with the PI, are responsible for designing user-friendly CRFs, based on the study protocol. The CRF will be reviewed by DCC DM, Biostatisticians, and Systems Developers for design and logic.

Upon finalization of the CRF design, the PD, CSC or designee uploads the CRFs (via the study tracking system) to the DCC.

The DCC reviews the CRFs and assigns variable names to each data field (*i.e.*, annotates the CRFs).Standardized data field names will be used when possible. Following annotation assignment, the DCC DM Director and Biostatisticians and CU, with support from the DCC Systems Developers, write and review these rules for the CRFs for logic and consistency; the rules provide range, logistical and consistency checks within and across the CRFs.

After reviews and corrections, the PD, CSC or designee uploads the annotated CRFs with rules to the DCC (via the study tracking system). The DCC Systems Developers review the annotated CRFs and rules. Any discrepancies or issues will be resolved with input from the PD, CSC, the DM Director and Biostatisticians. The preceding steps will be repeated until a final version is agreed upon.

The DCC Systems Developers create the data system by painting the data entry screens, implementing the rules and building the data entry user interface. During this phase of development, forms also are reviewed by the DCC DM Director and Biostatisticians.

After rules have been implemented, the DCC Systems Developers will validate the system with extensive testing.

Following system validation, the CU staff will independently test the system as an end user and the DCC Biostatisticians will test the system from an analytic standpoint. The PD, Protocol Director, and Systems Director will sign off and confirm the final agreed upon eCRF design and functionality.

2. How revisions are made, approved and filed?

Proposed revisions are discussed at the regular joint CU/DCC meetings and a decision regarding the disposition of each proposed revision is made.

New version numbers are assigned when any form modification change the data that are captured or alters the behavior of the system (e.g., increase/decrease in range of variable, addition of variable, deletion of variable, changes to drop down lists [outside of spelling corrections]). Minor version numbers are assigned when any form modification (e.g., spelling corrections or wording changes where denotation is not altered) do not require a change in the data captured or system behavior will be reflected in the version number after the decimal point (*e.g.*, version 1.01 compared to version 1.0).

All proposed revisions to CRFs (or enhancements to the overall eDEMS) are uploaded to the DCC via the study tracking system per a request from the CU and/or DCC.

Resolution of each proposed revision is entered into the tracking system and constitutes the permanent record of each action related to each CRF. All changes are tested by the CU and the DCC to assure the change meets the request.

3. Who needs to sign-off and when?

All CRFs move through an extensive development phase wherein all versions are considered draft and sign off is indicated by moving to the next step in development (as outlined below).

- The CU signs off on the initial design of CRFs at the point when these are made available to the Data Management Group (via the study tracking system).

- The CU and Data Management Group sign off on an initial draft version (dated) of the CRFs following review, clarification of any questions, writing of rules and annotation. Sign off occurs at the point when the annotated forms are uploaded to the DCC (via the study tracking system).

- The DCC (Data Management and Systems Development) signs off on the final CRFs when a test version of the eDES is made available to the CU for end user testing.

- The CU and DCC (Data Management and Systems Development) sign off on the overall eDES when all issues noted during testing have been resolved.

After all testing is completed and all noted issues resolved, PD, Data Manager and Systems Director sign off on the eCRFs. This version is deemed final and labeled Version 1.0. (with date). At this point, any revisions require another sign off by appropriate parties, following thorough discussion of the need for a revision after data collection has been initiated. When changes are implemented, the form becomes Version 2.0 (with date). This process can continue as needed. However, the goal is to minimize the number of revisions on the CRFs and the eDES.

Appendix D contains a template for the sign off of certification eCRFs, final eCRFs and email notifications generated by the system.

5. Study Setup

1. Who will design and build the study?

The overall study design is the responsibility of the PI at the CU, in consultation with the DCC Director and/or Deputy Director regarding statistical issues.

The staff at the CU and the DCC will work collaboratively to build the study-specific data management infrastructure and systems in concordance with the study design.

2. *Computer system to be used (hardware and software)*

The primary tool for data capture is a web-based electronic data entry management system (eDEMS). This system, as part of a comprehensive application, was designed and developed at the UAB School of Public Health per the document 'General Principles of Software Validation; Final Guidance for Industry and FDA Staff', ucm126955.pdf, to meet FDA 21 CFR Part 11 guidelines. SOPs documenting the development process, IQ/OQ/PQ, system qualification, system validation, application validation plans, and validation test results are available.

SAS 9.2 (or subsequent versions) will be used to generate tables and summary statistics for reports including DSMB reports, as well as for data analyses.

3. *Data dictionary (outlining each data element, database references and validation)*

   Data dictionary is available upon request.

4. *Database design-output: printouts of database structures*

   Refer to ***Appendix E*** for database structures. Annotated CRFs are available on request.

5. *Entry screen design output: printouts of entry screens*

   Screen shots are available on request.
   (Located in S:\CASG_BAAs\11-0067\Programming\Documentation\Screenshots)

   Additional supportive documents:
   See S:\CASG_BAAs\11-0067\Programming\Documentation

6. *File loading outputs: specification, printout of code or configuration*

   File loading outputs available on request

7. *Audit trails:*
   - *Data:* All changes to data within DEMS (made by clinic, administrative, or other) are logged and clearly defined in the SOPs. All user activity is logged as well (*i.e.*, login attempts, selection of forms, etc.). Audit data are accessible to study administration (in read only format) and can be provided in human readable, electronic, or raw formats.
   - *DEMS:* All requests for modifications or additions to the DEMS are managed through the Tracking System. This application maintains an audit trail of request,

development, validation, verification, and status of any modification or addition to the DEMS.

- *IT Infrastructure:* All changes to servers, storage, or supporting software (*e.g.*, operating systems, SQL database engine) are logged. Manufacturer supplied patches to supporting software are maintained by Windows Software Update Service, Lumension/PatchLink, or in handwritten server logs maintained in UAB SOPH, Ryals 135.
- *Server and Application Events:* Windows event logs are remotely logged to an EventSentry logging system. Exceptional activity is emailed to IT administrative staff for timely monitoring. Exceptional activity would include, failed login attempts, password change events, services that halt, services that are started, hardware failures, temperature exceeding limits, or over committed resources.
- *Application Validation:* The Testing Framework maintains an audit trail of all test cases and their results.
- *Application Development:* Version control and archiving is managed using SourceSafe which also provides an audit trail of who checked out or checked in libraries from the archive.
- *Physical Security: See* ***Appendix H***

8. *Other systems to be configured*

a. Tracking System: All requests for modifications or additions to the DEMS are managed through the Tracking System. This application maintains an audit trail of request, development, validation, verification, and status of any modification or addition to the DEMS. The Tracking System Manual of Operations is available on request.

b. Database Interface for Laboratories: Depending on the data requirements (real-time vs batch), laboratories will be provided with a data entry interface or a mechanism for uploading an Excel spreadsheet with results. Regardless of the mechanism for inclusion in the study database, all laboratory data will be checked in real time for adherence to pre-specified ranges as well as logic and consistency checks.

6. CRF Workflow

Table 1. Schematic of Study Design for 11-0067 (Gan Premie)

(NOTE: Required Studies in Black Font, Optional Studies in Blue Font								
	Period 1(Study Assessment Days 1 - 3)	Period 2 (Study Assessment Days 4 - 10)[a]	Period 3 (Study Assessment Days 11- 17)[a]	Period 4 (Study Assessment Days 18 -24)[a]	Period 5 (Study Assessment Days 25 -31)[a]	Period 6 (Study Assessment Days 32 -38)[a]	Period 7 (Study Assessment Days 39 - 42)[a]	
Baseline demographics[b]	X[c]							
Hematology labs[d]	X[c,e]	X[e]	X[e]		X[e]	X[e]	X[e]	X[e]
Chemistry labs[f]	X[c,e]	X[e]	X[e]		X[e]	X[e]	X[e]	X[e]
Creatinine	X[g]	X[e]	X[e]		X[e]	X[e]	X[e]	X[e]
Ganciclovir pharmacokinetics	X[h]				X[i,j]			
Virology blood specimens for CMV viral load[k]	X[l]	X[l]	X[l]		X[l]	X[l]	X[l,m]	X[l,n]
CMV detection from noninvasive urine specimen	X[o]	X[o]	X[o]		X[o]	X[o]	X[o]	X[o]
Ganciclovir dosing information	X[p]	X[p]	X[p]		X[p]	X[p]	X[p]	X[p]
PRBC transfusion assessment	X[q]	X[q]	X[q]		X[q]	X[q]	X[q]	X[q]
Assessment for AEs or SAEs		X	X		X	X	X	X
Total volume of blood required for study procedures	1.75 mL	0.5 mL	0.5 mL		0.5 mL or 1.5 mL[i]	0.5 mL	0.5 mL	0.5 mL

a) Data and specimens in this column to be captured if subject still receiving ganciclovir as clinical treatment
b) Gestational age at delivery, date of birth, day of life at initiation of IV ganciclovir therapy, gender, race, ethnicity, birth weight, weight at enrollment, length in centimeters at enrollment, reason ganciclovir being administered, ganciclovir dose and dosing frequency, manufacturer of the ganciclovir lot utilized at the treating facility, date ganciclovir therapy was initiated
c) Window: Birth through Study Assessment Day 3)
d) WBC with differential, hemoglobin, platelet count. Optional laboratory draws are not required by the protocol, and so no documentation on a source document will be required.
e) If being drawn for clinical reasons; any laboratory value obtained during the window will suffice, with an effort being made to capture the most abnormal value. Optional laboratory draws are not required by the protocol, and so no documentation on a source document will be required.
f) AST, ALT. Optional laboratory draws are not required by the protocol, and so no documentation on a source document will be required.
g) To be drawn on the calendar day that ganciclovir PKs are being drawn. Study related laboratory draws will be delayed or deferred if the investigator believes that obtaining them might increase subject risk. Additionally, a study-related laboratory specimen that is unevaluable due to clotting or laboratory related issues will not be repeated. If a study related laboratory draw is delayed or deferred, study staff will document this on a source document.
h) Ganciclovir concentrations will be obtained with one of the Study Assessment Doses 3, 4, 5, 6, 7, or 8 (Window: Study Assessment Day 1 through Study Assessment Day 5) at the following time points: 0h (immediately prior to IV ganciclovir dose; window: -15 min), 1h (immediately after the end of the IV ganciclovir dose; window: +15 min), 2-3h, 5-7h, and 10-12h; required amount of whole blood for plasma ganciclovir determination at each time point is at least 200µL (0.2 mL). Study related laboratory draws will be delayed or deferred if the investigator believes that obtaining them might increase subject risk. Additionally, a study-related laboratory specimen that is unevaluable due to clotting or laboratory related issues will not be repeated. If a study related laboratory draw is delayed or deferred, study staff will document this on a source document.
i) If desired by the treating physicians, ganciclovir concentrations may be obtained around one dose during the window at the following time points: 0h (immediately prior to IV ganciclovir dose; window: -15 min), 1h (immediately after the end of the IV ganciclovir dose; window: +15 min), 2-3h, 5-7h, and 10-12h; required amount of whole blood for plasma ganciclovir determination at each time point is at least 200 µL (0.2 mL). Optional laboratory draws are not required by the protocol, and so no documentation on a source document will be required.
j) If subject weighs < 575 grams, the second set of PK draws cannot be performed (would exceed blood draw parameters of 7 mL/kg over 42 days)
k) To be obtained only once per study period; ideally, at least 72 hours should separate viral loads being obtained in different study periods
l) Required amount of whole blood for CMV PCR is at least 0.5 mL. Study related laboratory draws will be delayed or deferred if the investigator believes that obtaining them might increase subject risk. Additionally, a study-related laboratory specimen that is unevaluable due to clotting or laboratory related issues will not be repeated. If a study related laboratory draw is delayed or deferred, study staff will document this on a source document.
m) If subject weighs < 600 grams, the virology specimen for CMV viral load will not be performed (would exceed blood draw parameters of 7 mL/kg over 42 days)
n) If subject weighs < 650 grams, the virology specimen for CMV viral load will not be performed (would exceed blood draw parameters of 7 mL/kg over 42 days)
o) Urine collection will be non-invasive (e.g., bagged, indwelling foley catheter, excess clinical specimen, etc.). If urine is obtainable, it will be frozen and sent to the UAB Central Laboratory for processing. If an attempt to obtain urine for CMV detection is unsuccessful, study staff will document the failed attempt on a source document.
p) mg/dose, dosing interval, subject weight
q) Once during each Study Period the study team will record the number of PRBC transfusions received by the study subject since enrollment (for the Period 1 documentation) or since the last recording (for documentation for Periods 2-7). A PRBC transfusion is defined as ≥ 10 mL/kg of PRBCs within a 24 hour period.

Within 3 days after the end of a study period, the user will enter data in the eDES from source documents (specific guidelines provided in the protocol specific MOP) collected at the time of the visit.

Systems Workflow
Guides the user through the form selection process; directing them to the appropriate forms, notifying them when a form is available, incomplete, required, overdue, or not due until a future date. Features are implemented through 'rules based' decision engine that can alter the Work Flow based upon the state/relationship of any set of data points contained within the study database as the data are entered. That is, the work flow mechanism not only can control how the user navigates the form menus, it could also dictate that a user must complete a subsequent form at the very moment the user enters data that defines a SAE condition.

7. Data Entry

The Central Unit will develop an *eDES User Manual* for site use and will be reviewed by the DM Director and Biostatisticians.

Each site participating in this study will be required to identify at least one research staff member to enter data. The staff member entering data into the eDES will be required to obtain certification through the DCC/CU for using the system and for entering study data onto the eCRF from Source Document Worksheets (SDW) or other source documents.

Preparation for the eDES certification process will take place after the following occurs:

- Version 1.0 of the eDES has been implemented.
- The CSC, other Central Unit administrators and/or Central Unit study coordinators will develop certification packet for three test subjects.
- The three test records will be entered into the test eDES site by data management team entities: Central Unit, Data Management and Programming. Records from all 3 sources must match. Otherwise, corrections will be done appropriately. When all records from 3 sources match, the records will then be matched to the corresponding paper forms to ensure all data entered correspond to the data on the certification packet. Corrections are made, if necessary. Otherwise, "gold records" have been established. Gold records will be used as the basis for comparing and grading the records entered by a person undergoing certification.

The following is a description of the certification process:

- Site PI or designee will provide, by email, to the CU CSC the name of the research staff member designated for entering data at the investigator's site.

- The *eDES User Manual* will be provided to the investigator's site prior or with the certification process. This document provides written guidance on the use of the eDES.
- The PD or designee will grant permissions by email for the designated user to access the eDES test site. In the CU, two staff members are granted responsibility to provide password access for appropriate access. The CSC or designee will send to the user one of three Test Subject Packets (#1, #2 or #3) that will be used to enter data into the eDES training site.
- After the user enters the test subject, the user will notify the CU stating entry completed and providing the PID#1 and #2. The CU will forward this message to the DCC including the information on which Test Subject Packet was used for certification for assessment of accuracy of data entry. A report will be generated by the DCC and sent to the CSC or designee at the CU.
    - If the user has an error rate less than or equal to 0.5%, the user will have passed the training and will be certified to enter data into the eDES.
    - If the user has an error rate greater than 0.5%, the user will be required to repeat the certification process.
- If the user passes the certification process, the CU will send email notification to the user and will change the user's permissions from test to active and will include a certificate of successful completion
- If the user fails to pass the certification process on his/her first attempt, the CSC or designee will send a different Test Subject Packet to the user.
- If the user fails to pass after three attempts, one of the following will occur:
    - Site PI will be asked to identify another member of his/her team to enter data
    - The user will be asked to review the eDES user manual and wait one month before re-attempting the certification process.
    - The user will participate in a one hour training session and then re-attempt the certification process.
- If a site fails to enroll any subjects within 6 months of certification, the user will recomplete the certification process to assure skills and knowledge of use of the eDES remain current.
- When new users are identified, each will be required to complete the certification process. The CU will manage this task.

Monitoring Data Entry: Except for the PK series day, eCRFs must be completed and locked within 7 days of the visit. For visits when the PK series is completed, eCRFs must be completed within 48 hours of the visit. A Form Completion report will be generated by the DCC, containing information on missing eCRFs based on visit schedule. Reports on the number of requests for unlock and deletion of records will also be generated on a regular basis. In addition, reports on late visits also will serve as a guide to monitoring eCRF data entry.

8. Data Cleaning

1. Edit check specifications

Validation: The system will indicate to the user those fields that do not meet predetermined conditions, defined as rules. Validation rules have four components: trigger condition, message, background color, and type. Rules are grouped by their type, where type defines when a rule is processed and what occurs when a rule is triggered. New rule types can be created as needed. Example rule types that are processed during data entry are:

a. *Soft rule:* Changes the background color of the field in question, presents the user with a message specifying the expected range, asks the user to verify the data entered as correct, and accepts the data into the system. If this is a lab value, an alert will appear requesting completion of an AE if NCS is not selected.
b. *Hard rule:* Changes the background color of the field in question, presents the user with the range of acceptable values or provides a reason why the entry is unacceptable, and will not accept the data into the system. Form cannot be locked without administrative override.
c. *Administrative approval*: Changes the background color of the field in question, presents the user with the range of acceptable values or provides a reason why the entry is unacceptable, and will only accept the data into the system after administrative authorization. *Administrative approval* will be by the PD or PI.

Validation rules are executed when a form is opened, as data are entered, and when a form is 'locked.' The ability to 'lock' a form is an optional feature in the eDES and, when enabled, it is presented to the user on the form tool bar as a button labeled 'lock.' A form is 'locked' when the user can click on the 'lock' button and no validation messages are presented. A 'locked' form is considered complete, correct, contains no data deemed unacceptable by a validation rule, and cannot be changed ('unlocked') without the intercession of a study administrator. Feature is implemented through a 'rules based' decision engine that can provide validity checks based upon the state/relationship of any set of data points contained within the study database (*i.e.*, any data, such as within the same form/visit, encompassing different forms from different visits, data from different participants, data from an inventory, etc).

Refer to ***Appendix F*** for the rules for the eCRFs rules.

2. *Data management self evident corrections*

- *Skip Patterns:* Based on pre-existing data, guides the user through a form, primarily to prevent users from entering illogical/irrelevant data, but can be used for other purposes as well. For example, if data in the system indicates the participant is male, the system will not allow the user to answer subsequent questions concerning how many pregnancies the participant may have had. There may be questions for clinic personnel regarding active enrollment that applies when specific targets are met. Another use not related to data quality would be the case where a clinic may need to respond to questions regarding drug orders based on inventory data. Feature is implemented through a 'rules based' decision engine that can alter the data entry flow based upon the state/relationship of any set of data points contained within the study database (*i.e.*, any data, such as within the same form/visit, encompassing different forms from different visits, data from different participants, data from an inventory, etc.)

3. *Study-specific discrepancy (query) handling guidelines*

   Protocol dictates that all queries are to be submitted through the Request for Supplemental Information (RSI) System when indentified by the CU which provides the means for documenting both requests and responses to requests. Reports on RSIs will be generated regularly and discussed during the scheduled meetings. RSIs must be responded to by appropriate site in a timely manner.

   Possible data entry errors identified by statistical analysis based on data from locked eCRFs will be documented and submitted to CU containing relevant information. The CU will review and send an RSI to the appropriate site if necessary. The site will take the appropriate actions to address this query (e.g., request CU to unlock a field).

4. *Query flow and tracking including process for editing data*

   RSI System: Provides a form-based system, with supporting audit trail, for study management to communicate with the clinic personnel. Typically used for managing data queries between study management and clinics.

   Independent Monitor Role:
   Data monitors will review data at the site as required by the Clinical Monitor Plan for this protocol. eDES contains self-documenting mechanisms to support site monitoring. Persons (CRA) assigned a site monitor role can login to the system (with read only rights to data for the assigned site) and review data using the same screens as the user who entered the data. Access will be provided by the CU for a span of 3

weeks. Monitors can create comments for specific fields. Monitors and the CU administration will be able to generate a list of queries and comments generated by the Monitor. Sites will be able to print a list of Monitor queries. When the user (site personnel) log in, the user is presented with a list of site monitor observations along with appropriate tools to address each observation individually. Study administrators have the ability to review these exchanges from within the Administrative System.

Central Unit PD and CSC Role:
The Central Unit PD and CSC or designee can generate RSI, based on information obtained in oversight of the clinical sites. For example: queries may be needed to be sent to the sites following review of site timeliness of eCRF entry, subject visits outside of windows, errors impacting lab shipments, logic checks of submitted data, etc.. The CSC or designee will be able to generate RSIs via the eDES by logging into the system and generating an RSI for the site to review. Sites need to regularly check the RSI listing in the eDES to view any new or pending RSI. The system allows for the site user to provide a response. When the RSI is resolved the CSC and PD can designate that the RSI is 'resolved'.

9. Handling Safety Data

1. AE reconciliation
   Adverse events are entered, saved and/or locked. If an AE is locked, the end user requests the PD, CSC or designee to unlock the form for updating with new information.

2. ISM Procedures
   Following development of the Independent Safety Monitor (ISM) and requirements, guidelines will be provided for ISM report generation (content and frequency). Per ISM request, the DCC will develop draft report tables required for ISM review. ISM reports will be generated by the DCC under the leadership of the Protocol Director. The CU (the CSC, PI, PD) will review and comment on the ISM report. Final analysis and report will be agreed to by the PI and the Protocol Director.

10. Data Coding

Data for clinical signs and symptoms (*i.e.*, physical exams, AEs) are encoded using the most current version of MedDRA at the initiation of data collection. For consistency, the same version of MedDRA will be used throughout the data collection period (*i.e.*, newer versions when released will not replace previous versions).

Site users will be provided with a list of common expected adverse events that may occur during the course of the study for the specific disease under study. For this study the

common event names will be obtained from the DIAIDS Toxicity Table will be used as a guide for event names. The site staff may or may not use the terms.

11. Creating Reports

1. The following table lists the required external reports and their frequency:

Type of Report	Frequency	Month/Day (if applicable)
Semi-annual/annual DMID	Every 6 months	April 15 / October 15
ISM	Per ISM charter	TBD
Screening/enrollment activity per site	Monthly	By the 7th of each month
Protocol deviations	Monthly	By the 7th of each month
Number of Transfusions	Monthly	By the 7th of each month

2. The following table lists additional internal reports used by the CU and DCC:

Type of Report	Frequency	Month/Day (if applicable)
Failed screening	Monthly	By the 7th of each month
CRF completion rate and out of window visits per site	Bi weekly	By the 7th and 21st of each month
Endpoint completion	Monthly	By the 7th of each month

12. Transferring Data

1. The process for transferring the data to DMID will be obtained in writing with agreement between the DCC and DMID. The PI and COTR will confirm in writing agreement to transfer the data. All data to be transferred will be encrypted utilizing Federal Information Processing Standard Publication 140-2, (FIPS PUB 140-2).
2. compliant algorithms to provide an asymmetric encryption methodology that securely limits viewing of sensitive data to authorized persons only. Non-authorized individuals, including developers and system administrators, cannot access encrypted data.
3. Data will be transferred securely either via CD or electronically.
4. If DMID requests data be transferred in a format different than the one designed for this study, it will be necessary to determine if budget can accommodate the effort.

13. Closing Studies

Sites will be considered closed when:

- all queries have been resolved;
- all eCRFs have been completed and locked;
- monitors have completed Close Out Visits; and

- all specimens have been submitted to the UAB Diagnostic Virology Laboratory and the UAB Antiviral Pharmacology Laboratory.

Refer to ***Appendix G*** for the study closure checklist.

1. Locking the Database
   The database will be locked when the following occurs
   - all site queries have been resolved
   - all lab data has been included in the database
   - all sites have had study required close out visits by monitors
   - COTR provides instruction to lock the database

2. Database audit plan
   For the purposes of auditing the development processes of the database application, go to: S:\CASG_BAAs\11-0067\Documentation\SOPs
   Filename: 60_SOP_Validation_Project_Plan

   For the auditing mechanisms within the database:

Audit Trails

- *Data:* All changes to data within eDEMS (made by clinic, administrative, or other) are logged and clearly defined in the SOPs. All user activity is logged as well (*i.e.*, login attempts, selection of forms, etc.). Audit data are accessible to study administration (in read only format) and can be provided in human readable, electronic, or raw formats.
- *eDEMS:* All requests for modifications or additions to eDEMS are managed through the Tracking System. This application maintains an audit trail of request, development, validation, verification, and status of any modification or addition to the eDEMS.
- *IT Infrastructure:* All changes to servers, storage, or supporting software (*e.g.*, operating systems, SQL database engine) are logged. Manufacturer supplied patches to supporting software are maintained by Windows Software Update Service, Lumension/PatchLink, or in handwritten server logs maintained in UAB SOPH, Ryals 135.
- *Server and Application Events:* Windows event logs are remotely logged to an EventSentry logging system. Exceptional activity is emailed to IT administrative staff for timely monitoring. Exceptional activity would include, failed login attempts, password change events, services that halt, services that are started, hardware failures, temperature exceeding limits, or over committed resources.
- *Application Validation:* The Testing Framework maintains an audit trail of all test cases and their results.

- *Application Development:* Version control and archiving is managed using SourceSafe which also provides an audit trail of who checked out or checked in libraries from the archive.
- *Physical Security:* Server room and development offices require ID token to open electronic locks; hallways and server room have 24hr security camera. Electronic lock activation is recorded by campus security; video surveillance recordings are maintained a minimum of 30 days.

- Reports will be created to ensure all data have been entered and RSIs (from CU, DCC and monitors) have been properly addressed and all modifications have been made. A SAS program will be run to check for outliers, range checks, etc. Once all data-related issues have been resolved, the DCC informs CU that the database is ready to be locked for final analysis and reporting.

3. When the DCC determines that the data are clean and ready for analysis, the UAB CU PD will contact the COTR to request permission to lock the database and begin the process of analysis.

14. Security

Refer to ***Appendix H*** for the comprehensive security plan.

APPENDIX A

ALLOCATION OF DATA MANAGEMENT RESPONSIBILITIES

Data Coordinating Center (DCC)

Gary Cutter, PhD: Professor (Director)
Dr. Cutter is responsible for directing and supervising the activities of DCC personnel involved with this CASG study. He will provide statistical consultation on study design and protocol development and oversight of study implementation, study monitoring, quality assurance, statistical analyses, report generation and DSMB preparation.

Inmaculada Aban, PhD: Associate Professor (Deputy Director)
Dr. Aban is responsible for in overseeing the DCC activities and updating Dr. Cutter on the progress of the studies. She attends meetings related to protocol development and regular BAA team meetings with CU, DCC and Programming group. She is oversees in CRFs and eCRFs development and testing. She coordinates the clinical PIs on statistical issues related to the studies. She is the contact person in the DCC with respect to data requests from NIH and CU. She supervises the study statisticians in the development of CRFs and eCRFs in the early stage of the studies and eDES certification process.

Joan Hilner, MPH, MA: Program Director III (Data Management Director)
Ms. Hilner oversees and has direct responsibility for the day-to-day operations of the CASG DCC. She develops timelines for DCC tasks, direct staff in accomplishing goals and monitor progress through completion of milestones. She works closely with Drs. Cutter and Aban in oversight of all data management aspects of the project, including: (1) development and review of CRFs for the trials (annotation and system rules); and (2) developing, implementing and monitoring the quality control efforts for the trials. She interacts with the study leadership at the CASG Clinical Coordinating Center to ensure that all logistical aspects of the project are covered, without overlap between the two groups. She is responsible for resolving issues in a timely manner and ensure that that the data management aspects of the study are progressing in adherence with the study protocol. She has direct responsibility for review, approval and compilation of all documentation required for a FDA audit, including, but not limited to, documents prepared by systems, statistics and data management personnel. She is also responsible for tracking all training documentation for DCC personnel over the course of the trial. She attends regular BAA team meetings and work with virology and PK lab to develop database interfaces for receipt of samples and upload of analytic results to database.

Charity Morgan, PhD: Assistant Professor (Lead Faculty Statistician):
Dr. Morgan provides statistical and data quality support. She attends regular BAA team meetings. She plays an active role in the development of CRFs particularly in the writing of rules. She takes the lead role in the rigorous testing of eDES. She works closely with Kalyani Peri in this testing. She calls meetings with CU, DCC, and programmers to discuss results of eDES testing to help find resolution on the issues. She is in charge of the implementation of randomization schemes associated with the studies, where applicable. She participates in the

process of reviewing and finalizing the Data Management Plan and *eDES User Manual*. She and Dr. Aban will compile and finalize DSMB or ISM reports.

Kalyani Peri, MS: Statistician I (MS Level Biostatistician)
Ms. Peri attends regular BAA team meetings. She plays an active role in the development of CRFs, particularly in the writing of rules. She reviews CRFs and rules associated with CRFs. She performs eDES testing of rules in the CRFs and functionality with Dr. Morgan. She summarizes the results of the eDES testing from both the DCC and CU, and presents them to the team for discussion and resolutions. She uploads to the tracking system requests related to the testing of the eDES. She participates in the process of reviewing and finalizing the Data Management Plan and eDES user manuals. She and Ms. Kuo will work together in creating SAS programs to generate tables and statistics for data quality checks and reports.

Huichein Kuo, MS, MPH: Statistician I (MS Level Biotatistician)
Ms. Kuo is in charge of the certification process particularly in grading and giving feedback to CU on the results of the certification. She will work with Drs. Aban and Morgan in ongoing maintenance of the data analysis files and preparation of reports for site management, study committees, clinics, SMC and for feasibility analyses. Responsibilities will include compiling monthly databases; preparing monthly enrollment reports by race, ethnicity, and sex by site; preparing monthly SAE/AE reports and annual FDA reports (as required); assisting with data checks; working directly with Drs. Cutter and Aban and Ms Hilner on the safety monitoring and endpoint activities; working to assist with designing and re-designing programs to target cleaning and reconciliation of inconsistencies and anomalies across forms; and providing support for the production and publishing of the SMC Reports.

Richard Mailhot, MS, MBA: Systems and Information Technology Director
Mr. Mailhot is an integral member of the team that will design the electronic data entry management system (eDEMS). He will oversee the development, implementaton, and support of the eDES and web-based data management system. He will oversee routine maintenance as well as enhancements, amendments and changes to the web-based system, including changes to programming rules for data entry and quality control checking as a result of protocol changes or enhancements to site management tools. He also will oversee the development of the Systems Life Cycle documentation for the web-based systems and will work with Ms. Hilner to ensure that all systems testing is completed and documented in accordance with FDA regulations.

Christopher Parks, BS: System Analyst Sr. (Lead Systems Developer)
Mr. Parks will be the lead systems developer for the eDEMS. He will direct development work flows and After the first year, he will continue to work on managing requests for revisions, upgrades and enhancements to the systems as required. Additionally, he will assist Ms. Ilet Dale in the Central Unit in all aspects of the installation and implementation of the system at the clinic level and provide clinic support on computer/system issues as required. In addition, he will be responsible for developing and maintaining the study's administrative website and the change request system that will permit entry of requested changes and enhancements to the system and track the status of each to a final outcome. He will assist Mr. Chandel and Mr.Allcorn in creating the Systems Life Cycle documentation which is critical for any FDA audit; he will be repsonsible for updating the documentation as needed in Years 3-5.

Satpalsinh Chandel, MS: System Analyst (Systems Documentation Specialist)
Mr. Chandel will work with Mr. Parks and have primary responsibility for implementing design criteria along with testing eDES and the study's administrative website. He will work closely with development team, quality assurance analysts, and other documentation staff to research, learn and document MITS suite of applications. He will develop documentation and then translate that into materials to be used in training the clinical sites. He will also be responsible for creating technical documentation of Software Development Life Cycle (SDLC) for eDEMS in compliance with "CFR 21" which is critical for any FDA audit.

Charles Allcorn: System Analyst (Systems Developer)
Mr. Allcorn is the primary and lead systems developer for the eDEMS Testing Framework. He will design and implement changes to the Testing Framework to match changes in the eDEMS that arise during the projects life cycle. His responsibilities also include managing test case development and work flows once the study protocal has been established and eDEMS URS has been handed over to MITS from the CU. He will assist Mr. Chandel in creating the Software Development Life Cycle documentation which is critical for any FDA audit; he will be repsonsible for updating the documentation as needed in Years 3-5.

Central Unit (CU)
Penelope M Jester, BSN, MPH: CU Program Director
Ms. Jester will oversee the CU staff in the development, implementation and assessment of the protocol. She will coordinate efforts with the Virology Laboratory, Pharmacology Unit and Data Coordinating Center related to protocol development, implementation and assessment, maintaining continuous and open communication with all entities. She is responsible for reviewing and assuring that protocol-specific endpoints are being met and for assuring that contractual deliverables are completed within the protocol and sponsor required timelines. Additionally, she assists in all report generation, providing review and comment. Ms. Jester is the interface with NIH, with the regulatory and the monitoring contractor, and with the pharmaceutical partner. Ms Jester will oversee that all UAB CU staff have the proper training and certification for their job tasks. She manages all personnel involved in clinical administration, and regulatory management in the UAB CU for this study and directs close adherence to regulatory guidelines and GCPs. Ms. Jester works closely with Drs. Whitley and Kimberlin as key personnel for this study.

Bari Cotton, BSN, MA and Nancy Grady, BSN, CCRA: Clinical Studies Coordinators (CSC)
The CSC role includes (but is not limited to) assist with development of protocol manual of procedures, site quality management plans, review and provide guidance for informed consent completion and process, review and initiate problem resolution activity for site monitoring reports, safety reporting forms, and provide education and training to investigator and support staff for protocol implementation and follow up activity. The CSC oversees site adherence to Good Clinical Practices (GCP) and Code of Federal Regulations (CFR). The CSC will continue to administer the clinical sites for this study. She also will participate in the biweekly protocol staff meetings as well as monthly and bi annual calls with study sites, reporting results of quality assurance activities. The CSA will continue to provide immediate clinical assistance to sites as well as regular protocol training. She will implement monthly calls with site staff. The CSC will review all monitor reports in real time and provide appropriate corrective action. The CSC will

assist with report generation and report review. The CSC will work closely with Ms. Jester and Dr. Kimberlin.

APPENDIX B

DATA ANALYSIS PLAN

Study Hypotheses

Our primary hypothesis is that ganciclovir pharmacokinetics and pharmacodynamics in premature infants with postnatally or congenitally acquired CMV infection differ from those in term neonates and older infants.

Sample Size Considerations

The primary outcome used for power analysis is the area under the curve for 12 hours (AUC12) following 6 mg/kg of ganciclovir. In a one-way ANOVA design, we would like to compare the means of 4 groups with sample sizes of 8, 8, 8, and 8. If the means of the AUC12 of the 4 groups are 20, 20, 30, and 35 assuming a common standard deviation of 10, these mean differences (equivalent to an effect size of 0.72) will be detected at 83% power using an F test with 0.05 level of significance. In order to look at other possible scenarios, we provide the table below that looks at other standard deviation values, its corresponding effect size given the differences in means as described above, and the power of detecting such a difference/effect size.

Standard Deviation	**S=8**	**S=9**	**S=10**	**S=11**
Effect Size	0.81	0.72	0.64	0.59
Power	96%	91%	83%	75%

The above parameter values were hypothesized based on results from other studies.[25,34] It is worth noting that there are no PK data in this population and the results are likely to be different from other studies due to the maturational changes.

Subjects will be stratified by gestational age and by chronologic age as follows: 1) ≤ 27 weeks 6 days gestational age at birth and ≤ 30 days chronologic age at study enrollment; 2) ≤ 27 weeks 6 days gestational age at birth and > 30 days chronologic age at study enrollment; 3) ≥ 28 weeks 0 days gestational age at birth and ≤ 30 days chronologic age at study enrollment; 4) ≥ 28 weeks 0 days gestational age at birth and > 30 days chronologic age at study enrollment.

Data will be collected on standardized case report forms. Standard non-compartmental techniques will be used initially to estimate pharmacokinetic parameters derived from the ganciclovir concentration-time data. The resource utilized for pharmacokinetic analysis is WinNonlin version 5.3, Pharsight Corporation, Mountain View, CA.

Planned Interim Analyses

There are no planned interim analyses or safety reviews for this trial.

Final Analysis Plan

Primary analysis: To compare the ganciclovir pharmacokinetics and pharmacodynamics as measured by AUC12 in premature infants with postnatally or congenitally acquired CMV infection differ from those in term neonates and older infants, we will utilize mixed models for repeated measures. Additional pharmacokinetic parameters that compose analyses for secondary endpoints include Cmax, T1/2,CL, and VD. In addition to being able to compare these outcomes

for the different groups, we can also look into how these measures change over time and adjust for covariates.

Ganciclovir pharmacokinetic parameters will initially be determined using non-compartmental analysis (WinNonlin v5.3) for each individual subject. The parameters (AUC_{12}, CL, Vd, etc.) will be summarized and further used for exploratory pharmacodynamic analysis. We will also apply pharmacokinetic models to the concentration-time data, either individually or using a population approach. We may also pool these data with prior CASG 109 PK data in order to have a more robust covariate analysis across a wider range of ages.

The second pharmacokinetic analysis will utilize either population pharmacokinetic or individual modeling approaches, depending upon how much data we actually are able to collect and the nature of those data. Concentration-time data will be analyzed using nonlinear mixed-effects in ADAPT 5.0. If a population approach is employed, this will give us the opportunity to explore relationships between ganciclovir exposure and multiple covariates, such as gestational age, weight, renal function, etc.

A 95% confidence interval will be constructed to evaluate the mean changes in the log of the viral load between baseline (day 1) and weeks 1, 2, 3, 4, 5, and 6. Area under the curve will be calculated for each subject's CMV viral load measurement utilizing the trapezoidal rule. These AUCs will be calculated over the entire course of drug administration. Spearman's correlations will be given for each AUC estimation and also for the AUC after baseline viral load (VL) adjustment. Analysis of variance will be used to investigate whether grouping AUCs into groups (undetected, 100-1000, 1000-10000 and $\geq$ 10000) would indicate any PD relationships. In addition, changes in CMV viral load from baseline over time (weeks 1 through 6) will be correlated with PK parameters. These data will provide the framework for all PD analyses, where ganciclovir exposures variables will be correlated with the response variables using linear or maximum effect PD models.

Secondary analyses: To investigate the association of secondary outcomes namely, neutropenia, CMV in urine, viral load and resistance to ganciclovir, with plasma concentration, we will utilize inference methods based on Generalized Estimating Equations (GEE) which models repeated binary data. As in the primary analysis, GEE will enable us to compare groups, investigate changes of outcomes over time, and adjust for any covariates.

APPENDIX C

USER REQUIREMENT SPECIFICATIONS DRAFT

Specifications

1. User Database Design and Functionality

1.1. The user database has four primary purposes:
- 1.1.1 To provide a secure mechanism to control password access and permissions.
- 1.1.2 To provide the ability to generate and control enrollment and/or randomization (including study drug assignment) and protocol specific emails to the correct research personnel.
- 1.1.3 To provide a repository for maintaining contact information for investigators and key research staff.
- 1.1.4 To generate distributions lists per protocol from the database.

1.2. Fields required for the user database are listed below:
- User's name
- Selection of title of user (PI, Sub I, study coordinator, regulatory, monitor, laboratory personnel, administrator, other)
- User's email address
- Protocol(s) user is permitted access to Institution site staff member associated with (site #)

1.3. Design of the user database
- 1.3.1 Design data entry page to include contact information fields listed in 10.1.2. and when required, assignment of permissions
- 1.3.2 Design the contact database to meet the requirements listed in 10.1.1

1.4. Functionality of the user database will be the following:
- 1.4.1 Entry of contact information will be managed remotely by the CU PCII or designee.
  - 1.4.1.1 The PCII or designee will be given permissions to assign a user access by the PD or designee.
  - 1.4.1.2 After entering user information, the PCII or designee will assign a user name and a temporary password.
  - 1.4.1.3 After the user enters the system with the user name and temporary password, the user will be prompted to create his/her own confidential password.
  - 1.4.1.4 If the user forgets his/her password, she/he will contact the PCII or designee to receive a temporary password in order to re-identify a confidential password.
  - 1.4.1.5 Types of permissions:
    - Access to subject enrollment/randomization and eCRF completion

- Access to print study-specific documents
- Access for monitoring purposes
- Access to unlock eCRF for data query resolution
- Access to enter specimen results
- Access for user certification of eDES usage
- Access to generate queries

1.4.2 Email notifications (see 1.4.5) will be sent to designated study personnel. These personnel will be identified by the PD and or designee.

1.4.3 The PCII or designee will be able to de-activate users when personnel discontinue participation in the protocol.

1.4.4 The content of the email alerts and notifications will be drafted by the PD or designee

1.4.5 Types of notifications

1.4.5.1 Enrollment notification to site

1.4.5.2 Shipping of PK samples notification to CU and to pharmacology lab

1.4.5.3 Shipping of virology samples notification to CU and virology lab

1.4.5.4 PK eCRF field change notification to Pharmacologist

1.4.5.5 Protocol deviation alert to CU

1.4.5.6 Shipping receipt acknowledgment alert for Virology specimen

1.4.5.7 Shipping receipt acknowledgment alert for PK specimens

1.4.5.8 PK result notification

1.4.5.9 Data field unlock request

1.4.5.10 Transfusion alert

2. End User Training and Certification

2.1. Purpose

2.1.1 To build an electronic system that will include a means for remote data entry by end user, email notifications when required, interface use with ancillary services and a system for monitoring.

2.1.2 To verify the functionality of the eDES

2.1.3 To assure user is capable of using the eDES.

2.2. Process for verifying the eDES

2.2.1 Comprehensive testing will take place reviewing and testing functionality of each feature in the eDES.

2.2.2 PD and designees will be granted permission to test the system when system/functions are complete.

2.2.3 Each eCRF field will be tested to determine if the assigned rules are functioning as required.

2.2.4 At least three UAB CU clinical personnel will test the system by reviewing and testing each field of the eCRF by entering mock data, assuring functionality is as required and confirming that the rules are correct. Additionally, DCC staff will also test the fields.

2.2.5 After completion of the testing of the eCRF fields, email notifications, ancillary service users, the PD or designee, MITS and DCC will confirm that eCRF and eDES meets specifications, design and functional requirements.

2.2.6 The PD will sign off after confirmation by all entities that the system meets the URS.

2.3. Process for certifying end users: Clinical Sites

2.3.1 Central Unit staff will prepare 3 mock sets of Source Document Worksheets (SDW) (test packets). Each set will be assigned a number: #1, #2 and #3.

2.3.2 Three staff (1 from the CU, 1 from Programming group, 1 from the Data Management group) will be identified to enter each of the three test packets.

2.3.3 A DCC biostatistician will compare the records entered by all 3 users to the corresponding packet. Errors and problematic fields will be identified and corrections made as determined necessary by the CU clinical administrators, MITS and DCC.

2.3.4 Following successful completion of the 3 test packets entry and 100% assurance of system functionality, the 'gold records' are established. Gold records are used to compare the records entered by a person undergoing eDES certification consequently determining if the person passed or failed the certification.

2.3.5 The PD or designee will create a user manual for end users (*eDES User Manual*)

2.3.6 Users identified by the PD or designee will be provided with the *eDES User Manual* and provided with access for certification by the PCII or designee, as needed.

2.3.7 The designated Biostatistician will identify successful data entry certification as less than or equal to 0.5% error rate.

2.3.8 The CSA or designee will provide user with #1 test packet. The PD, PCII, or designee will assign data entry permissions to the user.

2.3.9 Following entry of the #1 test packet into the eDES, a DCC Biostatistician will report to the PD or designee if the user's error rate was no greater than 0.5%. (The DCC will also provide a list of errors.) The PD or designee will generate to the user a certificate of successful entry of the test packet.

2.3.10 If the user fails to successfully enter #1 test packet (*i.e.*, error rate was greater than 0.5% error rate), the list of errors will be reviewed by the PD or designee with the user, and the PD or designee will re-train the user on how to avoid those errors. The PD or designee will provide the user with #2 test packet.

2.3.11 If the user fails to successfully enter #2 test packet, the process in 2.3.11 will be repeated. The user will be provided with #3 test record. If #3 test packet is not successfully entered, the CU administrators and the DCC will discuss options for the clinical site. These may include requesting another

person at the site assume the site's data entry responsibilities, or request the user who failed data entry begin the certification process again in 1 month. A final option will be for the CU administration to provide an hour long training session on use of the eDES to the person who has failed certification three times. Note that a site will be activated only if at least one staff member has successfully showed the capability to correctly enter data (*i.e.*, passed certification).

2.4. Process for certifying end users: Monitors
- 2.4.1 A test site will be created for the monitors to demonstrate the use of the monitor function of the eDES.
- 2.4.2 The PD or designee in collaboration with MITS will create a user manual for the monitors use (*eDES User Manual: CRA)*
- 2.4.3 The CRA will review the *eDES User Manual: CRA* and will review the system with the PD or designee.
- 2.4.4 The PD or designee will document the training.

2.5. Process for certifying end users: CU
- 2.5.1 A mock site will be created for the CSA and designee to test and practice entry of data queries into the eDES system and to test opening and locking the system for site data entry.
- 2.5.2 MITS will create a user manual for the CU Administration use (*eDES User Manual: CU Administrators).*
- 2.5.3 The PD and designee will review the *eDES User Manual: CU Administrators* and will review the system with MITS.
- 2.5.4 MITS will document training of the CU Administration.

3. Enrollment Design and Functionality

3.1. Purpose of the enrollment component of the eDES system is the following:
- 3.1.1 To allow for remote enrollment of subjects who meet study entry criteria.
- 3.1.2 To notify all key personnel in a timely manner of successful enrollment.
- 3.1.3 To disable enrollment in a cohort if enrollment is completed for that cohort.
- 3.1.4 Patient Identification (PID) numbers will be assigned: screening PID will be assigned after selecting New Subject. Enrollment process (completion of inclusion/exclusion criteria) can begin after PID #1 (4 alphanumeric characters) is assigned. Enrollment PID #2 (5 numbers) will be assigned when subject successfully meets protocol required eligibility criteria for enrollment.

3.2. Design of the enrollment component of the eDES
- 3.2.1 The inclusion and exclusion criteria will match the protocol.
- 3.2.2. The criteria will be answered 'yes', 'no', 'NA', and/or have defined ranges, if number values for study entry are required. The PD or designee will manage and oversee that the design of the entry criteria match the protocol eligibility requirements for the eDES.

3.2.3 The PD or designee will provide wording for successful enrollment email notifications and will identify the personnel to whom this email will be sent.

3.2.4 Assignment order of screening PIDs will be created by the designated biostatistician and MITS.

3.3. Functionality of the enrollment component of the eDES

3.3.1 When preparing to enroll a subject, the end user will select "New Subject". The PID #1 will be assigned prior to entering eligibility criteria.

3.3.2 The end user will have the option to save or lock responses to entry criteria

3.3.2.1 ***Save:*** data entered will be saved but will not be used to enroll/randomize a subject into the study and will not activate a screening notification email. The responses can be updated and edited as needed.

3.3.2.2 ***Lock:*** the user has determined the eligibility data entered into the database are acceptable, and believe successful screening enrollment can occur. After locking, the data cannot be altered.

3.3.2.3 Should a site need to alter responses to the screening entry criteria, the end user must request an unlock of the specific field in question. The PD or designee will unlock the form and permit the data to be amended. If this request takes place after the subject has started study required activities, the user may need to amend more than the entry criteria. This will require a meeting.

3.3.3 The enrollment criteria can be locked if all inclusion criteria are not met. However, no additional eCRFs will be available for use, since the subject did not meet enrollment criteria.

3.3.4 Enrollment schematic

3.3.4.1 Enrollment in this protocol will be stratified based on gestational age and enrollment age. The groups are as follows:

1) ≤ 27 weeks 6 days gestational age at birth and ≤ 30 days chronologic age at study enrollment;
2) ≤ 27 weeks 6 days gestational age at birth and > 30 days chronologic age at study enrollment;
3) ≥ 28 weeks 0 days gestational age at birth and ≤ 30 days chronologic age at study enrollment;
4) ≥ 28 weeks 0 days gestational age at birth and > 30 days chronologic age at study enrollment.

3.3.4.2 Enrollment will cease after 8 subjects are enrolled in a group.

3.3.5. Functions that occur after successful enrollment

3.3.5.1 Confirmation of successful enrollment will appear on the computer screen immediately.

3.3.5.2 Email notification of successful enrollment will be sent to key study personnel immediately to the site and others as designated by the PD or designee. The notification will include PID#1,#2, site number, PI name.

3.3.6 Failure to successfully complete enrollment of a subject
3.3.6.1 If the form is locked without successfully meeting enrollment, all eCRFs in the periods will not be accessible (cannot view or open).
3.3.6.2 Detailed eDEMS alert(s) will appear if the user failed to successfully answer the eligibility criteria in such a way that permits enrollment. The details will appear, specifying/ identifying the first criteria on the list of inclusion /exclusion criteria that prevents enrollment.
3.3.6.3 Alert will appear requesting that user complete a protocol termination/completion form if informed consent has been signed.

4. CRF Design and Functionality

4.1. Purpose of CRFs
4.1.1 To provide rigorous and accurate collection forms for recording data abstracted from source documents as per protocol specifications.
4.1.2 To minimize the possibility of error in data collection.

4.2. Design of eCRFs
4.2.1 eCRF format will be designed by the PD or designee and reviewed by the site staff or other designated CU representative.
4.2.2 eCRF format will be compared to the protocol-specific schedule of events, the narrative in the protocol, and the MOP for accuracy
4.2.3 eCRF format will be reviewed by DCC to provide guidance on feasibility of design and confirm accuracy and to assign data field names (annotate).
4.2.4 Source document worksheet forms will be prepared and designed to match the eCRF
4.2.5 The following will be the process for eCRF development
4.2.5.1 CSA or designee develops each required eCRF. Itis reviewed by a second CU administrator.
4.2.5.2 DCC reviews and assigns data field names (annotation)
4.2.5.3 CU and DCC assign rules and reviews before form is finalized
4.2.5.4 Appropriate version number with date is attached to the forms.

4.3. Functionality of eCRFs
4.3.1 eCRF may be ***saved*** prior to locking if the user has not completed the eCRF to their satisfaction
4.3.2 eCRF when ***locked*** may not be changed unless the user submits a request to unlock form for editing.
4.3.3 PD or designee will unlock the form if a change is requested by the user.
4.3.4 A change request will be made by the user accessing the locked eCRF and selecting: ***request to unlock.***
4.3.4.1 This selection will then allow the user to provide a detailed reason for the request to make a change to the locked eCRF data field or form.
4.3.4.2 The eDEMS system will generate an email to the PD or designee to unlock the specific form and data field or form.

4.3.4.3 If the PD or designee confirms the need to unlock the eCRF page, s/he will administratively unlock specific data field or form
4.3.4.4 Following updating the data field(s) the user will lock the eCRF again.
4.3.4.5 Changes will be tracked electronically in the database to provide a 'paper trail' for changes.
4.3.4.6 Information will be retained in the database noting who made the change, what the change was and when the change occurred.

4.3.5 Sites will have the ability to print the locked eCRF.

4.3.6 'Same data fields' between eCRFs will be linked/ autopopulated to assure no discrepancy occurs.

4.3.7 Adverse event form
4.3.7.1 If an AE is reported it may be locked if the event is ongoing. Each time eCRFs are completed, the end user will be notified that ongoing AEs are present.
4.3.7.2 The AE form can be opened and updated. When an event is resolved or resolved with sequelae, the form cannot be opened by the site without requesting permission from the CSA or designee.

4.3.8 Unscheduled eCRF: forms that may be used at any time as needed during the course of the study
4.3.8.1 Additional comments page
4.3.8.2 Protocol deviation (refer to section 10.6)
4.3.8.3 PBRC transfusion page
4.3.8.4 Adverse event page
4.3.8.5 Protocol completion/termination (for use when subject has not completed last dose of study drug). Following completion of this form, all forms after this visit/phase will not be accessible.

4.3.9 Site wide forms: forms that are used that are not subject-specific or contain multiple subject data.
4.3.9.1 Protocol deviation (refer to section 10.6)
4.3.9.2 Additional comments page
4.3.9.3 Specimen shipping form (virology and pharmacokinetic)

4.3.10 Subsequent forms: select forms that must be completed before proceeding
4.3.10.1 Following administration of last dose of assessment dose drug, all CRFs will be inaccessible until completion of Protocol Termination/Completion found in the Subsequent forms menu.
4.3.10.2 Completion of this form makes all forms accessible

5. CRF Query Design and Functionality

5.1. Purpose of Query Design and Functionality

5.1.1 The purpose of the query system is to track all requested changes to the CRF system

5.1.2 The query system is managed/tracked in three ways:
5.1.2.1 for monitor queries for issues identified during interim monitor visits

5.1.2.2 for CU queries based on review of data, logic checks, non-data related queries, or feedback from Biostatisticians, based on results of data quality check

5.1.2.3 for internal review site queries and edits a site requires based on internal review

5.2. Design of Query System

5.2.1 For Monitor Query

5.2.1.1 Monitors will be trained to use the system via review of a training certification manual

5.3.1.2 Monitors will be given password access to the eDES system in order to review and comment on data fields on the locked eCRF. The access will be granted for 7 days prior to each visit and will be active for 14 days after each visit. The monitor supervisor might also be provided with access.

5.2.1.3 Monitors will be able to print a list of the queries they have identified.

5.2.1.4 Monitors will be able to print resolution to each query

5.2.1.5 Monitors will be able to generate a query about a data field and the site user will be able to provide an electronic response in the system.

5.2.2 For Central Unit query

5.2.2.1 The CU CSA or designee may generate queries

5.2.2.2 Queries will be the result of site activity review, logic checks, non-eCRF issues, feedback from Biostatisticians, etc.

5.2.3. For site query and resolution

5.2.3.1 The site user may identify an error based on internal review of reported data

5.2.3.2 Site user must have a means to request a change in data that will be tracked by requesting an unlock.

5.3. Functionality of the Query System

5.3.1 For monitor query

5.3.1.1 Monitor receives password access within 1 week prior to site visit and up to 2 weeks after the visit

5.3.1.2 At the IMV, the monitor logs into the eDES and access site and then subject eDES.

5.3.1.3 In reviewing source documents and source document worksheets, compared to eCRF, monitor notes a discrepancy between the source and the eCRF reported data. Monitor is able to select specific data field requiring a comment, click on the field and enter a comment that requires a response by the site user.

5.3.1.4 The monitor will be able to print a list of comments she/he generates

5.3.1.5 The site end user will be alerted to an outstanding monitor comment/query on the entry page to the eDES (monitor query for a form is highlighted)

5.3.1.6 The site end user clicks on 'Monitor Query' icon, selects highlighted subject. Site user will then see a forms page with highlighted eCRFs that have comments with monitor queries highlighted noting a query/comment was generated. Site user clicks on the highlighted eCRF and will view the eCRF with the field(s) highlighted that have pending comments/queries. Clicking on the highlighted field will allow the user to view the query, to write in a response and to select unlock if needed.

5.3.1.7 As needed, the PD or designee will unlock the data field requested if determined to be necessary by the end user; the site user will amend the data if appropriate, and relock the eCRF.

5.3.2 For CSA query

5.3.2.1 The CSA or designee will access enter the eDES through the Administration site and select 'RSI' option

5.3.2.2 A comment or query will be generated identifying if the comment/query is site based, or subject based (selecting for the correct subject and then specific form, and form field)

5.3.2.3 The site end user will be notified by an alert that shows up as soon as they login to the eDES.

5.3.2.4 Via a 'discussion' page, the chain of communication will be noted between the CSA or designee and site user until resolution of the query.

5.3.2.5 The site users credentials will be linked to his/her log on id

5.3.2.6 Action that may take place may include unlocking the eCRF for amending the data. This will be tracked.

5.3.2.7 The PD or designee will note that the query is resolved

5.3.3. For site query and resolution

5.3.3.1 Site end user will be able to request an unlock of a data field if a change is requested

5.3.3.2 Site end user will click on unlock and then select a specific data field to be unlocked and a rationale for data change will be entered.

5.3.3.3 A request to unlock a data field will generate an email to the CSA or designee

5.3.3.4 Following change to the data by the site user, the CSA or designee will review and will note if still outstanding or if resolved.

5.3.3.5 Following resolution of changed field, the end user will lock the form

6. Protocol Deviation Design and Functionality

6.1. Purpose of protocol deviation reporting

- 6.1.1 To assure deviations from the protocol are reported in a timely manner.
- 6.1.2 To assure protocol deviations are reviewed at the CU in a timely manner
- 6.1.3 To assure the end user identifies all required Protocol Deviations at the end of each visit

6.2. Design of the protocol deviation reporting

- 6.2.1 Data fields for the protocol deviations will be defined by DMID
- 6.2.2 PD or designee will provide to MITS the fields for the PD CR
- 6.3.2 PD or designee will provide to MITS the rules for the PD eCRF data fields
- 6.3.3 PD coordinator or designee will review the PD form within 24 to 48 hours of when locked in order to query within a timely manner as directed by the protocol.

6.3. Functionality of the protocol deviation reporting

- 6.3.1 The PD form may be saved if form is not completed by the user; it must be completed properly to be locked.
- 6.3.2 The user can select 'site wide' protocol deviation which will allow for completion of a PD that does not link to a subject.
- 6.3.3 eDES tracks all PDs generated from eCRFs for each visit via eCRF form F90. User must open this form and locked to be able to enter data for subsequent visits. By locking this form, the user acknowledges the need to complete at PDs in the list to complete the data entry for that particular visit.
- 6.3.4 Changes to the entered and locked eDES
  - 6.3.4.1 The PD or designee may unlock the eDES database if requested to do so by the user.
  - 6.3.4.2 The eDES database will document and track changes that were made and by whom the changes are made.

7. Failed Screening Design and Functionality

7.1. Purpose

- 7.1.1 To track the number of subjects pre-screened by a clinical site during the implementation of a clinical study.
- 7.1.2 To identify reasons for failed screening to assess feasibility and implementation barriers of the clinical study
- 7.1.3 To track a clinical site's screening activity

7.2. Design of Failed Screening
- 7.2.1 Design of the eDES will be based on CU requirements for failed screening.
- 7.2.2 No personal health information will be recorded in the failed screening page.
- 7.2.3 Failed screening pages will be protocol specific
- 7.2.4 The PD or designee will provide rules for each field.
- 7.2.5 A listing will be generated in real time that includes the following fields:
  - Site name and /or site number
  - Per month and cumulative:
    - Months with no screenings
    - Number of failed screenings per month

7.3. Functionality of Failed Screening
- 7.3.1 User will access the failed screening page in the eDES following pre-screening of a patient who does not meet eligibility criteria or at the end of each month
- 7.3.2 Entry of information may be done in real time or at the end of the month.
- 7.3.3 All fields will be required to be completed prior to locking the failed screening information.
- 7.3.4 The completed form will be printable and will contain an assigned record number.
- 7.3.5 The listing of failed screening will be printable

7.4. Changes to failed screening
- 7.4.1 Site may request the Failed Screening eDES be unlocked by the CSA or designee
- 7.4.2 Changes will be tracked and documented in the eDES system.

8. Specimen Management Design and Functionality (for both Virology and Pharmacokinetic data)

8.1. Purpose
- 8.1.1 To provide direct entry of lab values (ie: viral loads, PK data) into the eDES
- 8.1.2 To provide entry of receipt of specimen shipment

8.2. Design of the specimen management
- 8.2.1 The design (specific data fields) will be directed by the protocol, the PD or designee and the lab director or designee.
- 8.2.2 Lab director or designee will enter the required data using a secure password.
  - 8.2.2.1 Entry of specimen receipt
  - 8.2.2.2 Entry of results

8.3. Functionality of the specimen management
- 8.3.1 With use of password access, the lab director or designee will enter required specimen data
- 8.3.2 Corrections to the entered data will be accomplished by requesting the PD or designee unlock the eDES.
- 8.3.3 Change, date and end user will be documented in the eDES system
- 8.3.4 The cumulative data will be printable.
- 8.3.5 Based on a request of the lab director, special programming and reporting from the data base may be necessary to provide results correctly. The lab director or designee working with the DCC will design the required functionality.

9. Administrative Function

9.1. Purpose
- 9.1.1 To provide functions for administrative oversight and management

9.2. Design of the Administrative Function
- 9.2.1 To provide the ability to review and manage data
- 9.2.2 To provide functions that are clearly tractable and adjudicated by the correct administrator with assigned responsibilities
- 9.2.3 To provide functions to assign user accounts and corresponding access type

9.3. Functionality of the Administrative Function
- 9.3.1 Per permissions, enter passphrase as needed (monthly)
- 9.3.2 Provide access for reviewing and updating MedDRA codes
- 9.3.3 Ability to delete and undelete forms
- 9.3.4 Ability to upload and download documents
- 9.3.5 Ability to generate and view queries (RSI)
- 9.3.7 Ability to view subject data
- 9.3.7 Ability to generate reports:
  - Demographics
  - Protocol deviations
  - AEs and SAEs
- 9.3.8 Unlock field and form approval
- 9.3.9 Ability to override approval
- 9.3.10 Ability to move documents on the test site.

10. Report Generation

10.1. Purpose
- 10.1.1 Due to requirements of the sponsor, certain reports are required to be generated routinely
- 10.1.2 Reports will provide information on site compliance

10.2. Design of the report

10.2.1 Required sponsor reports may include the following (this will be programmed in and generated routinely):

10.2.1.1 Enrollment information (monthly)
10.2.1.2 Protocol deviation listings (monthly)
10.2.1.3 UAB CU semi-annual and annual reports
10.2.1.4 DSMB reports (frequency determined by DMID, DSMB charter and protocol)
10.2.1.5 Failed screening and enrollment per site for real time access
10.2.1.6 Interim analysis, when applicable
10.2.1.7 Final study report (format determined by DMID)

10.2.2. Reports that provide information on site compliance:

- data error
- failed screening activity
- enrollment rate
- timely completion of eCRFs
- protocol deviations
- endpoint completion

10.3. Functionality of the report generation

10.3.1 For some reports, the CSA or designee will be able to print reports (as tables) in real time from the Administrative site:

- data error
- failed screening activity
- enrollment rate
- completion of CRFs within required window (within 3 days after end of each period)
- protocol deviations
- site activity (visit completion spreadsheet)
- per visit Protocol Deviation lists
- expected AE lists

10.3.2 For some reports, the report will be generated by the DCC Biostatisticians and the statisticians with review and edit as needed from the UAB CU:

- Interim analysis
- DSMB reports (open reports)
- Final study reports
- UAB CU annual and semi-annual reports
- Others as needed or requested

11. Locking the eDES Database

11.1. Purpose

11.1.1 To assure consistency in closing a database
11.1.2 To assure that data is clean when the database is locked

11.2. Requirements for the database lock
- 11.2.1 Prior to locking the database, final queries will be generated and resolved by end users
  - 11.2.1.1 PD or designee will provide documentation that all queries have been resolved
  - 11.2.1.2 DCC will assure no queries are outstanding
- 11.2.2 Prior to locking the database, all queries will be resolved
  - 11.2.2.1 PD or designee will assure all monitor close out visits will have been completed
  - 11.2.2.2 DCC will review the database to assure no queries are outstanding based on comments in the eDES
  - 11.2.2.3 PD or designee will review problem resolution forms and monitor reports as well as internal queries to assure all queries have been resolved.
- 11.2.3 Locking the database will be accomplished when the project officer provides in writing (email) that the database may be locked
- 11.2.4 Unlocking the database can only be done with written permission from the project officer and agreement from the statistician.

11.3. Archiving the eDES
- 11.3.1 The CU will be notified about where the databases will be stored
- 11.3.2 The CU will be contacted if there is a request for use of the database
- 11.3.3 The CU (with permission of the sponsor) may direct alternate disposition of the data pending necessary funding.

Definitions and Abbreviations

CRA	Clinical Research Associate
CU	Central Unit (clinical and regulatory management unit)
DCC	Data Coordinating Center (includes data management, statistical and programming and systems development support)
eCRF	electronic case report forms; information will be redacted from original source documents at the site
eDES	electronic Data Entry System; a web-based interface for data entry
eDEMS	electronic Data Entry Management System; this is the complete set of eCRF forms, email notifications, shared entry system with ancillary services
MITS	Multimedia Information Technology Service
PBMC	Peripheral blood mononuclear cell
PCII	Program Coordinator II
PCR	Polymerase chain reaction
PD	Central Unit Program Director
PK	Pharmacokinetic
PI	Principal Investigator
PID	Patient Identification
SDW	Source Document Worksheets

DOCUMENT HISTORY

Revision	Effective Date	Reason for Change

APPENDIX D

SIGN OFF SHEET FOR CERTIFICATION CASE REPORT FORMS (CRFs)

Protocol Title (Version Number and Date; DMID #): EVALUATION OF THE PHARMACOKINETICS AND PHARMACODYNAMICS OF GANCICLOVIR IN PREMATURE INFANTS RECEIVING TREATMENT FOR CYTOMEGALOVIRUS INFECTION (version 1.0 dated 25 Sept 2012, DMID Protocol #: 11-0067)

The following is an attestation that each CRF listed below used for Certification has met the required criteria for eDES development for clarity, completeness, functionality (as defined in the URS), testing, and supportive source document worksheets.

Form Number	Version Number	Version Date	Sign Off					
			Central Unit		Multimedia Information and Technology Systems		Data Coordinating Center	
			Date	Initials	Date	Initials	Date	Initials
F02	1.0	01/11/13						
F03	1.0	01/11/13						
F04	1.0	01/11/13						
F09	1.0	01/11/13						
F13	1.0	01/11/13						
F14	1.0	01/11/13						
F16	1.0	01/11/13						
F17	1.0	01/11/13						
F18	1.0	01/11/13						
F21	1.0	01/11/13						
F42	1.0	01/11/13						
F44	1.0	01/11/13						
F46	1.0	01/11/13						
F47	1.0	01/11/13						
F51	1.0	01/11/13						
F52	1.0	01/11/13						

*Forms that are unique to the virology lab director/manager or the pharmacologist will sign off on their required forms.

Printed Name	Responsibility/Role	Signature	Initials	Date

APPENDIX D (CONT.)

SIGN OFF SHEET FOR PRODUCTION CASE REPORT FORMS (CRFs)

Protocol Title (Version Number and Date; DMID #): EVALUATION OF THE PHARMACOKINETICS AND PHARMACODYNAMICS OF GANCICLOVIR IN PREMATURE INFANTS RECEIVING TREATMENT FOR CYTOMEGALOVIRUS INFECTION (version 1.0 dated 25 Sept 2012, DMID Protocol #: 11-0067)

The following is an attestation that each CRF listed below has met the required criteria for eDES development for clarity, completeness, functionality (as defined in the URS), testing, and supportive source document worksheets.

Form Number	Version Number	Version Date	Sign Off					
			Central Unit		Multimedia Information and Technology Systems		Data Coordinating Center	
			Date	Initials	Date	Initials	Date	Initials
F02	2.0	02/12/13						
F03	1.0	01/11/13						
F04	1.0	01/11/13						
F09	2.0	02/12/13						
F13	1.0	01/11/13						
F14	1.0	01/11/13						
F16	1.0	01/11/13						
F17	1.0	01/11/13						
F18	1.0	01/11/13						
F21	1.0	01/11/13						
F42	2.0	03/05/13						
F44	1.0	01/11/13						
F46	1.0	01/11/13						
F47	1.0	01/11/13						
F51	1.0	01/11/13						
F52	1.0	01/11/13						
F90								
F51B	1.0	01/17/13						
F52B	1.0	01/17/13						
F62A	1.0	02/15/13						
F62B	1.0	02/15/13						

*Forms that are unique to the virology lab director/manager or the pharmacologist will sign off on their required forms.

Printed Name	Responsibility/Role	Signature	Initials	Date

APPENDIX D (CONT.)

SIGN OFF SHEET FOR FINAL EMAIL NOTIFICATIONS

Protocol Title (Version Number and Date; DMID #): EVALUATION OF THE PHARMACOKINETICS AND PHARMACODYNAMICS OF GANCICLOVIR IN PREMATURE INFANTS RECEIVING TREATMENT FOR CYTOMEGALOVIRUS INFECTION (version 1.0 dated 25 Sept 2012, DMID Protocol #: 11-0067)

The following is an attestation that each email notification listed below has met the required criteria for eDES development for clarity, completeness, functionality (as defined in the URS), testing, and supportive source document worksheets.

Email Alert/ Notification	Version Number	Version Date	Sign Off					
			Central Unit		Multimedia Information and Technology Systems		Data Coordinating Center	
			Date	Initials	Date	Initials	Date	Initials
Enrollment	1.0							
PBMC transfusion	1.0							
Unlock request	1.0							
Protocol Deviation	1.0							
PK shipment	1.0							
PK receipt	1.0							
PK results	1.0							
PK variable change	1.0							
Virology shipment	1.0							
Virology receipt	1.0							

*Email alerts and notifications that are unique to the virology lab director/manager or the pharmacologist will sign off on their required forms.

Printed Name	Responsibility/Role	Signature	Initials	Date

APPENDIX E
DATABASE TABLE SCHEMA AND DATA MODEL

Location: S:\CASG_BAAs\11-0067\Documentation\SOPs
Filename: 90_Database Design

APPENDIX F

CRF RULES

Individuals completing eCRFs must be certified. Contact the CU to obtain access and guidance on training. An e*DES User Manual* will be available on the CU website providing guidelines for data entry, data lock and data correction. The data entry designee at each investigator's site must have reviewed and completed certification in order to be eligible for eCRF certification. Only persons participating in data entry training and having successfully completed test eCRFs (successful completion of the training course means 99.5% accuracy with test eCRFs).

At the end of each study assessment, complete each eCRF required. If data fields are not completed because a visit was not made or because a test was not done, indicate this by answering the applicable question on the eCRF page and complete a protocol deviation form, if applicable.

- Alpha fields should start on the left side.
- No trailing zeros are needed for alpha fields.
- Numerical fields should be filled so the data fields line up on the far right.
- Leading and trailing zeros must be used when completing numerical fields.
- For laboratory values unknown or not done do not enter all "9s" or "0s" in the space provided.
- The site is to use the following guidelines when estimating an unknown date: for the month use "6", for the day use "15", and for the year use "9999". Then complete the Add Comment eCRF indicating the date was estimated and document in the SD/SDW the estimated date, clearly indicating it was an estimation.
- If a subject's parent / legal guardian verbalize a general date. The site is to use the following guidelines: first of the month use "1" for the day, for middle of the month use "15" for the day, or for the end of the month use "30". For the begin of the year use "1" for the month , for the middle of the year use "6" for the month , for the end of the year use "12" for the month. Then complete the Add Comment eCRF indicating the date was estimated and document in the SD/SDW the estimated date, clearly indicating it was an estimation.

APPENDIX G

STUDY CLOSURE CHECKLIST FOR DATABASE LOCK

Task	Completed	Signed off	Date	Role
	Yes/No			
All queries resolved				
All site data 100% monitored at site				
All expected specimens received for PK analysis				
All expected specimens received for PBMC analysis				
All expected specimens received for virology analysis				
All PK analysis complete				
All PBMC analysis completed				
All virology specimens analyzed				
All culture specimens complete				
All required sequencing data completed				
PD contacts COTR to request database lock				

APPENDIX H

SYSTEMS SECURITY

The UAB CU DCC is committed to ensuring the privacy and integrity of the data and systems under its authority. Best practices dictate adequate security measures are achieved in a multi-layer approach: physical, electronic, application, detection, and response to breech and training.

- Physical security
  - Video surveillance of server room and hallways. System designed to maintain images for 30 days.
  - Environmental surveillance with two different systems (campus maintenance and DCC- provided systems). Both systems have automatic text and email notification when temperatures exceed proscribed limits.
  - Electronic locks on all doors providing access to servers. Campus security maintains log of use. Only authorized individuals can access secured rooms and rights are revoked upon termination of employment.
  - DCC policy is to physically secure all desktop PCs. Audit is performed annually to ensure compliance.
  - Onsite backup media is kept in secure room; offsite backup media is kept in fireproof safe in secure room.
  - PCs and laptops are placed so covered information is not publicly viewable.
- Electronic security
  - All laptop hard drives either owned by the institution or used for study purposes are encrypted using PGP.
  - All PCs used by developers are encrypted using PGP.
  - All PCs, laptops, servers have firewall, Patchlink, screensaver and an antivirus package installed and operational. These tools are centrally managed by IT administration.
  - Access to DCC PCs, servers, and managed applications require two factor login ID and password authentication. Login IDs are unique within application and not reused. GUIDS are unique within the DCC Active Directory and not reused. Current password policies are: passwords must be strong; passwords must be changed at least every 180 days; there must be at least six unique passwords before a password can be reused; and passwords cannot be shared.
  - Access to file systems and equipment is managed by group membership within the DCC Active Directory. Access is granted on a “least needed” basis.
  - Group membership is controlled by IT administrators, who will only respond to requests presented by known administrators.
  - Application and database servers will have Event Sentry software installed to provide secure remote logging and notification of exceptional events.

- Application
  - Applications are designed following the Clark-Wilson model. User credentials alone will not possess sufficient rights to access study data via any other means than the application provided.
  - Applications containing sensitive data will use FIPS compliant software to encrypt/decrypt the data. Passphrase and or keys will not be hard coded into the application; these must be held in memory. Decryption mechanism will remotely log access attempts to data it manages; logging mechanism will have filters that can be set to end alert messages to responsible administrators if access attempts exceed guidelines and have the ability to completely halt access to secured data.
- Detection
  - Campus IT Security operates twice daily scans of every computer on the network for known security risks, such as open ports, missing software patches, weak administrative passwords, and misconfigurations. When a computer is identified, campus security notifies the responsible system administrator and sets a deadline for remediation. In egregious cases, the network port supporting the computer will be shut off.
  - Campus IT Security operates network monitoring system which scans network packets for signatures of known malware, data streams addressed to known malware or suspect sources, or other anomalous (heuristic detection) network traffic. In the cases of known malware or known traffic to suspect sources, campus security will shut off the network port supporting the computer and notify the responsible system administrator. Anomalous network traffic is examined and may result in the shut off of the network port supporting the identified computer.
  - Applications employing decryption mechanisms (as described earlier) will remotely log access attempts to data it manages; logging mechanism will have filters that can be set to send alert messages to responsible administrators if access attempts exceed guidelines and have the ability to completely halt access to secured data.
- Security Response to Breech
  - It is institutional policy that all instances of data security breaches be reported to campus IT Security to initiate an investigation to document and determine the nature of the breech, what information is involved, how best to stop further loss, what remediation is necessary and if the breech is reported to authorities. Campus IT Security staffs an active response unit that provides forensics and maintains a close working relationship with State and Federal authorities.
- Training
  - All DCC employees take part in annual training regarding data security.
  - Application developers are required to read the “Application Development Guidelines SOP” and provide signed affirmation.

- Application developers are required to read and stay abreast of the guidelines provided by Open Web Application Security Project (www.owasp.org).
- Any proposal having DCC participation as data management will address the need for observing best security practices at the client endpoints.

Risk Analysis Form

MITS

January 24, 2013

Version 1.0

APPROVALS			
Name	**Title**	**Signature**	**Date**
Satpalsinh Chandel	Main Author		
Christopher Parks	Reviewer		
Charles Allcorn	Reviewer		
Richard Mailhot	Director		
	Principal Investigator (PI)		

Disaster Prevention and Recovery Plan

MITS

January 31, 2013

Version 2.0

APPROVALS			
Name	**Title**	**Signature**	**Date**
Satpalsinh Chandel	Main Author		
Christopher Parks	Reviewer		
Charles Allcorn	Reviewer		
Richard Mailhot	Director		

Server Recovery Procedure

MITS

January 31, 2013

Version 2.0

APPROVALS			
Name	**Title**	**Signature**	**Date**
Ralph Lewis	Main Author		
Christopher Parks	Reviewer		
Charles Allcorn	Reviewer		
Richard Mailhot	Director		

FDA 21 CFR Part 11 Compliance

Validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records.

- Web-based systems created via MITS Suite include a Testing Framework for creating, executing, and documenting comprehensive test cases of the eDEMS.
- MITS Suite has an exhaustive set of SDLC SOPS which include IQ/OQ/PQ and Validation Project Plans along with a validation summary report that documents the validation and verification of MITS Studio, and eDEMS produced.
  - Records entered by clinic personnel contain a checksum that provides the ability to discern invalid or altered records. All changes to data within eDEMS (made by clinic, administrative, or other users) are logged and clearly defined in the SOPs. All user activity is logged as well (*i.e.*, login attempts, selection of forms, etc). Audit datasets are accessible to study administration (as read only) and can be provided in human readable, electronic, or raw formats.
- The ability to generate accurate and complete copies of records in both human readable and electronic form suitable for inspection, review and copying by the agency.
  - The administrator has the ability to grant access to the agency for inspection, review and copying records in human readable or electronic forms
- Protection of records to enable their accurate and ready retrieval throughout the records retention period.
  - Application operates on redundant supporting systems; backups of data are maintained on tape for five years or as required by contract agreement. System security and backup process is described in Risk Analysis SOP, Disaster Prevention and Recovery Procedures SOP, Infrastructure SOP.
- Limiting system access to authorized individuals
  - Access to a system is limited to specific users via login ID and passwords where a given user is required to not only have an appropriate login ID and password but must also belong to an authorized security role/group. Request to allow access must come from recognized project management.
- Use of secure, computer-generated time stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records. Record changes shall not obscure previously recorded information.
  - The eDES and Administrative systems maintain log files that record changes to the data (including creating new records, modifying records and deletion of records), who made the changes and when the change was made.
  - The log files will keep a cumulative record of all changes made in the history of the database and maintain a non-obscured view of previous information recorded.
- Use of operational system checks to enforce permitted sequencing of steps and events, as appropriate.

  - *Skip Patterns:* Based on pre-existing data, guides the user through a form, primarily to prevent users from entering illogical/irrelevant data, but can be used for other purposes as well. For example, if data in the system indicates the participant is male, the system will not allow the user to answer subsequent questions concerning how many pregnancies the participant may have had. There may be questions for clinic personnel regarding active enrollment that applies when specific targets are met. Another use not related to data quality would be the case where a clinic may need to respond to questions regarding drug orders based on inventory data. Feature is implemented through a 'rules based' decision engine that can alter the data entry flow based upon the state/relationship of any set of data points contained within the study database (*i.e.*, any data, such as within the same form/visit, encompassing different forms from different visits, data from different participants, data from an inventory, etc.)
  - *Work Flow:* Guides the user through the form selection process; directing them to the appropriate forms, notifying the user when a form is available, incomplete, required, overdue, or not due until a future date. Feature is implemented through 'rules based' decision engine that can alter the Work Flow based upon the state/relationship of any set of data points contained within the study database as the data are entered. That is, the work flow mechanism not only can control how the user navigates the form menus, it could also dictate that a user must complete a subsequent form at the very moment the user enters data that defines a SAE condition.
- Use of authority checks to ensure that only authorized individuals can use the system, electronically sign a record, access the operation or computer system input or output device, alter a record, or perform the operation at hand.
  - Applications are designed following the Clark-Wilson model. User credentials alone will not possess sufficient rights to access study data via any other means than the application provided.
  - Access to subcomponents of system and associated data is controlled through hierarchical security group membership.
- Use of device checks to determine, as appropriate, the validity of the source of data input or operational instruction.
  - Where required access to systems is limited by IP address restrictions and machine ID.
- Determination that individuals who develop, maintain or use electronic record/electronic signature systems have the education, training, and experience to perform their assigned tasks.
  - Individuals who develop, maintain, or use electronic systems are required to have the following education, training, and experience to perform their assigned tasks:
    - User training
    - Administrator training
    - Developers will have the following background:
      - IRB training

- Technical training (either certificate or college degree as evidence)
- Mentoring by more senior staff on an existing projects
- Prior work experience
- Knowledge of GCP

- The establishment of, and adherence to, written policies that hold individuals accountable and responsible for actions initiated under their electronic signatures to deter record and signature falsification.
  - Each project that employs an electronic system created/maintained by MITS will have a corresponding SOP, outlining roles and responsibilities for individuals associated with the project.

  Use of appropriate controls over systems documentation, including:
  - Adequate controls over the distribution of, access to, and use of documentation for system operation and maintenance.
    - Documentation related to the development process and project management is kept in Source Safe along with the source code or in file systems associated with the project. Access to these resources is limited to authorized personnel, which is controlled via login ID, password and membership in an appropriate security group.
    - Documentation required by users, such as user manuals, are kept in secured file systems that are available via the eDES and require appropriate login ID, password and membership in the controlling security group.
  - Revision and change control procedures to maintain an audit trail that documents time-sequenced development and modification of systems documentation.
    - Development documentation is maintained in a document management system (Source Safe).
    - Changes to eCRFs will be documented by corresponding annotated CRF template that describes the layout, verbiage, validation rules and skip patterns required by the project management. Annotated CRF templates will be maintained in the project file system for the life of the project. To distinguish between versions of a given CRF, version number will be displayed in a prominent location on the form.
    - Documentation is maintained in file systems, with access governed by security group membership.
    - File systems are backed up nightly and archived monthly.
    - All changes to the systems are recorded in the Request Tracking system. This system documents the process by recording the request, who made the request, who assumed the responsibility of implementing the request, when the request was ready for testing, which developer(s) performed validation and their result, and which user performed verification and the result. Where paper CRF forms can be employed to outline and document the test procedure

these forms are signed and dated by the tester and maintained for the life of the project. Where tests produce electronic data records, these records are created in "Test" database and kept for the life of the project.

- Testing of new forms/applications (or changes to forms/applications) are logged in the Request Tracking system. Testing is performed by the assigned primary programmer, secondary programmer, and from the project management staff before the work is released to end users. Testing is performed against a test database that mirrors the production database and any records created during testing process are maintained in test database for the life of the project.

- Sec. 11.50 Signature Manifestations
  - Signed electronic records shall contain information associated with the signing that clearly indicates all of the following:
    - the printed name of the signer;
    - the date and time when the signature was executed; and
    - the meaning (such as review, approval, responsibility, or authorship) associated with the signature.
  - The items identified in paragraphs above shall be subject to the same controls as for electronic records and shall be included as part of any human readable form of the electronic record.

- Sec. 11.70 Signature/Record Linking
  - Electronic signatures and handwritten signatures executed to electronic records shall be linked to their respective electronic records to ensure that the signatures cannot be excised, copied or otherwise transferred to falsify an electronic record by ordinary means.

- Subpart C: Electronic Signatures
  - Requirements related to electronic signatures (e.g., §§ 11.50, 11.70, 11.100, 11.200, and 11.300)
    - Unique and not reassigned to another individual.
    - Individuals are identified as prior to assigning credentials and their record will contain information regarding the date and time the signature was executed, the printed name of the signer and their meaning associated with the signature.
    - Two component signature: login ID and password. Login IDs are unique to each individual.
    - Individuals must sign in with their login ID and password for each use of the system.

- The printed name of the individual that enters data is displayed by the data entry screen throughout the data entry session. This avoids the possibility of a different individual inadvertently entering data under someone else's name.
- Individuals are instructed to not share or record passwords.
- Passwords are stored in an encrypted format within the system.
- Within a single application, the system inherently prevents two or more individuals from sharing identical login ID.

Document/Revision History

SOP Revision #	Effective Date	Description of Changes	Superseded Document #

1. Purpose

The purpose of this SOP is to define the most important aspects of the data management process for research studies:

1. Identify the work to be performed
2. Identify the individuals (or group) responsible for the work;
3. Identify applicable procedures and guidelines;
4. Outline required documentation or output to be collected or produced**.**

2. Responsibilities

The Data Coordinating Center is responsible for documenting data management practices for a particular clinical trial in a Data Management Plan.

3. Procedures

3.1 The Data Management Plan (DMP) documents the framework for the management of data for a particular clinical trial. Refer to SOP 401: Data Management for further detail concerning the various aspects of data management.

3.2 Each study should have a DMP.

3.3 The DMP should be written at the beginning of the study.

3.4 The DMP for a study should provide direction regarding the following topics:

3.4.1 Responsibilities and Scope of Work
3.4.2 Data Analysis Plan
3.4.3 CRF Design
3.4.4 Study Setup
3.4.5 CRF Workflow
3.4.6 Data Entry
3.4.7 Data Cleaning
3.4.8 Handling Safety Data (AEs and SAEs)
3.4.9 Data Coding
3.4.10 Creating Reports
3.4.11 Transferring Data
3.4.12 Closing Studies
3.4.13 Security

3.5 Refer to Appendix 4.1 for a DMP template (including topic descriptions).

3.6 The DMP should be revised whenever significant changes to existing processes are implemented (e.g. process change or computer application change).

4. Appendix

4.1 Sample DMP Template