Chapter 2

VATS Overview

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INTRODUCTION

The main resource for this study is the formal VATS Protocol. The objective of this section of the manual is to guide VATS staff in the implementation, maintenance and data and specimen collection processes for the study. It is not intended as a substitute for any information included in the protocol. A brief orientation to and practical overview of the protocol by sections follows. The remainder of the manual contains detailed information on data and specimen collection not included in the VATS protocol, as well as an administrative section.

SECTION 1 -- ENROLLMENT

2.1.1 ELIGIBILITY

Criteria for inclusion and exclusion are listed in section 3 of the protocol. The VATS will keep a screening registry for all ineligible cases. We would like to be able to describe the population not entered. To standardize across sites, coordinators should screen (complete Form 1 for) all patients who are known to be HIV positive, have no prior transfusion history and for whom the first transfusion is planned.

Form 1 data should also be collected on all patients who are screened but not eligible (or not randomized). **If a patient is found to be ineligible, then the subject initials should be left blank on the form in order to insure patient privacy**. At the minimum the following Form 1, Section B eligibility questions should be answered: B1-B5, B11a, B11b, B15 and B21. All other eligibility questions for which the answers are also known should be answered. It is acceptable to leave other information blank. The coordinating center will not send edits on ineligible patient Form 1's with missing information.

Coordinators should only screen patients they expect will be transfused within 72 hours. If more than 72 hours elapse between screening and randomization, the patient must be re-screened. If more than 72 hours elapse between randomization and the enrollment transfusion, the Coordinator should follow the procedure outlined in Communications Memorandum #5. This Memorandum (located in Appendix I of this section) also outlines the procedure to follow for randomized patients who are retrospectively found to be ineligible.

CMV serostatus: Since prospective CMV screening of study components will not be performed, HIV positive patients must also have a confirmed history of either testing positive for the CMV antibody serologically, OR a past or current CMV end organ disease diagnosis, to be eligible for this study. Testing prior to entry may be required to confirm the patient's CMV sero-status. Each site should have a procedure in place to obtain and run this test. Results of this test will not be reported on VATS data collection forms, but should be kept in the patient's study file as verification.

NOTE: CMV stratification for randomization purposes is according to end-organ disease history alone, not serostatus. Therefore, although serologically CMV antibody positive, patients without confirmed history of CMV retinitis or GI disease, for example, will be stratified as "NO" prior CMV disease.

2.1.2 RANDOMIZATION

Randomization occurs in two stages and cannot be performed without the necessary information for CD4 (or lymphocyte count) and CMV end-organ disease stratification. Complete instructions on randomization are located in section 4 of the protocol, as well as chapter three and Forms 1 and 2 question by question specifications in this manual. Briefly, after determining a patient is eligible:

Clinical Coordinator:

- calls coordinating center at NERI
- receives 5 digit randomization number
- records the number on Forms 1 and 2
- Sends Form 1 to NERI
- Keeps bottom(pink) copy of Form 2 and brings the white and yellow copies to the transfusion service

Transfusion Coordinator (or designee):

- decodes 5 digit randomization number into treatment group
- indicates treatment arm on Form 2
- sends white copy of Form 2 to NERI in postage paid envelope provided and keeps yellow copy in a secure place to maintain the treatment blinded status of clinical coordinators and transfusion physicians.

Treatment arm allocation tables will be provided to the transfusion coordinator at each site. These will be sent directly from NERI and are also to be kept in a secure area with access limited to transfusion service staff trained to randomize, prepare and/or issue VATS study components. Transfusion coordinators are responsible for routinely monitoring the table and the study component issue records (Form W-1) in order to quality assure correct randomization and study component issue for VATS treatment arms.

In case of telephone failure, clinical coordinators will assign randomization codes from sealed envelopes provided by NERI.

SECTION 2 -- PRODUCT PREPARATION, ADMINISTRATION & BLINDING

2.2.1 OVERVIEW

VATS Study Components/Products include red cell products and platelets.

VATS Blinded Study Components, i.e., treatment arms, include leukoreduced and non-leukoreduced red cell products.

Leukoreduced (i.e., leukocyte reduced) red cell units are defined as red cell units containing $\leq 5 \times 10^6$ leukocytes.

Each site needs to create and maintain an adequate inventory of VATS red cell study components:

- Non-leukoreduced units AND
- Pre-storage leukoreduced ($\leq 5x10^6$) units
- $\leq$14 days of age; always issue the unit(s) closest to 14 days of age first
- Blood Group O or A
- CMV pre-screening not required

Note: Every effort should be made to comply with component type and age requirements in the VATS Protocol including use of an alternate supplier, if need be.

2.2.2 PROCESS OF PREPARATION AND ISSUE OF STUDY COMPONENTS

The process of preparation and issue of study components is as follows:

For blinded red cell components

1) The VATS participant's study ID number will be needed. Refer to VATS Randomization table: identify the appropriate treatment arm for that participant (ID)
2) Select the appropriate leukoreduced or non-leukoreduced red cell component that is closest to, but not more than, 14 days of age from the VATS study inventory.
3) If **non-leukoreduced**: collect a 1 ml. Whole Blood donor segment, label and store.
   If **leukoreduced**: Locate, or if applicable, request from your supplier, a donor segment associated with the unit.
4) Transfer the leukoreduced or non-leukoreduced unit to a study bag; label as required by Federal/state/institutional regulations; affix a VATS unit label. It is recommended that the unit # and patient's study ID number are recorded on the VATS label as a means of linking a particular study patient to a particular unit at the time the unit leaves the transfusion service. However, sites may elect to track this information in another way.

5) Take a 1 ml. specimen from the bag and split into two tubes (0.5 ml each), label and store.
6) Weigh the issue bag
7) Attach a VATS Transfusion Monitoring Form 43 to the unit, or one of the units.
8) Complete paperwork (after or concurrent with preparation): Donor/Specimen Processing Form(s) (a separate form for each unit issued), Segment Request Form (if needed), Weekly Summary of Activity

Note: Aliquots obtained from the transfer/issue bag at the time a component is issued should be frozen as soon as possible, preferably the same day the component is transferred and issued for transfusion. The maximum is 72 hours from the time of issue. It is also important that a well mixed sample is obtained from the transfer/issue bag.

If a patient has been withdrawn from blinded red cell components and will be receiving open label, leukoreduced red cells:

Follow instructions for leukoreduced blinded components above, skipping step 4.

It is important that the transfusion coordinator communicates cases of patients being withdrawn from blinded components to staff issuing study components. It is suggested that the information and date of withdrawal be documented on the randomization table (see step 1), next to the patient's VATS study ID number.

2.2.3 OTHER COMPONENTS: STUDY AND NON-STUDY

Platelets are the only other blood product that are being tracked and monitored as part of the study; therefore platelets are the only non-red cell blood product being considered as a study component.
Receipt of all other non-study components, such as cryoprecipitate, plasma, etc. will be tracked on the "Weekly Summary of Activity" sheet, but not monitored.

2.2.4 PLATELET PREPARATION, ETC.

- All Platelets are to be leukocyte filtered, and filtered at the blood bank or transfusion center, unless an emergency situation prevents it.
- Apheresis platelets are preferred, but the freshest platelets available should be issued.
- Donor segments will not be collected; however, two 0.5 ml aliquots will be collected at the time of issue from each apheresis unit or pool (preferably single donor), labeled and stored (per step 5 of blinded red cells).
- Transfer to a study bag and a VATS label are not required for platelets.
- Follow steps 6-8 as listed for blinded red cell components.

2.2.5 BLINDING

Everyone outside of the transfusion center will be blinded to the treatment arm of VATS participants.

The Randomization Table needs to be kept in a secure area with limited/controlled access, as does the "Weekly Activity Summary". If the summary is computerized at your site, the VATS transfusion medicine MD. must not have access to files containing treatment arm information.

Study issue bags need to have the VATS label attached and not contain any information regarding its leukocyte status, i.e., leukoreduced or not.

Issued components and segments/ specimens obtained must be able to be linked with the donor unit ID number and the recipient's VATS patient ID number. This information will be recorded on both the Donor Specimen Form 42 (to be sent directly to NERI from the transfusion service) and the Transfusion Monitoring Form 43 (issued with study components). Because they contain treatment arm information, Forms 2 (Blood Bank Randomization) and 42 will be sent directly to NERI from the transfusion service and copies kept in a secure area. As with the randomization table and weekly summary sheet, it is important that, unless a patient's treatment arm is intentionally unblinded, contents of these two forms are kept confidential within the transfusion service.

It is important to note that a patient can go off study components without anyone being unblinded to what was previously received. Only the Transfusion physician for the VATS can make the decision to withdraw a patient from study components or unblind the treatment arm. However, since it is important that clinical and transfusion service coordinators are informed about these decisions, in addition to the transfusion physician, coordinators will be required to sign the study form reporting these occurrences, before it is sent to NERI.

SECTION 3 -- CONCOMITANT THERAPIES

2.3.1 -- OVERVIEW

With the exception of the few medication related eligibility exclusions, VATS will not prohibit or mandate any changes in clinical or therapeutic management of participants. However because they may affect study virologic measures, additions of some drugs within 2 weeks following the first two transfusion episodes is strongly discouraged. A complete list of these and other concomitant medications are located in Section 6 of the protocol. Information on select medications will be obtained at the baseline and quarterly visits.

SECTION 4 -- STUDY DEFINITIONS

2.4.1 -- OVERVIEW

The VATS Steering Committee and sub-committees have developed specific end-point related definitions to be used in a standard fashion across all VATS sites. These include definitions and/or criteria for “serious” HIV related complications (definitive and presumptive), transfusion reaction (definite and possible) and transfusion episode, among others. VATS definitions are located in Section 7 of the protocol and need to be accessible to staff completing VATS medical record abstracts and transfusion event forms.

2.4.2 HIV DISEASE PROGRESSION

It is important to note that a primary objective of the VATS involves counting "serious HIV-related complications". These consist of selected AIDS defining conditions from the CDC’s 1993 list and serious bacterial infections which have a median survival of <1 year or acute mortality of >5%. Sites are to forward documentation of a subject’s first event, i.e. “serious HIV-related complication” to NERI. Documentation of subsequent events must be readily available for review.

2.4.3 TRANSFUSION REACTIONS

(Definite/Possible) are defined in section 7.6 of the protocol. Clinical and Transfusion coordinators and physicians should always refer to this section when evaluating or reporting transfusion related signs and symptoms.

Clinical Coordinators need to keep count of within-subject transfusion events over time. A cumulative data collection form (Transfusion Event Form 44) has been created to facilitate tracking; however, coordinators may be asked to send copies of partially completed forms to the coordinating center periodically for distribution to the VATS DSMB for their review.

2.4.4 TRANSFUSION EPISODE

The first transfusion episode will always be associated with the baseline visit, i.e., typically the same day, or the day following randomization. A transfusion episode is measured by time rather than number of red cell units transfused. We are only concerned that the first two transfusion episodes are correctly delineated for a given patient to provide the most accurate serial blood test results to meet study objectives. A third transfusion episode would need to be counted if, for some reason, the pre-transfusion blood draw for the second episode is not obtained.

Although we are tracking and collecting data on them, platelet transfusions do not count as “transfusion episodes,” e.g., only the first and second red cell transfusions qualify as study related transfusion episodes. Pre and post blood draws are to be performed as scheduled for the first two transfusion episodes even if a patient is withdrawn from blinded study components, or the treatment arm is unblinded at any point prior to 28 days following the second transfusion episode. For example, if a patient is withdrawn from blinded study components during or following the first transfusion episode, serial blood draws would still be collected pre and post the patient's second episode, even though that patient is now "off study components" and receiving unblinded leukocyte reduced red cells.

Since serial blood draws will occur pre and post the first and second transfusion episodes, VATS staff need to be familiar with the definition and time interval constituting a single “transfusion episode.” Refer to section 7.1 for the definition and an example.

2.4.5 ON STUDY

Patients remain "on study" unless they withdraw their consent to participate, are completely lost to follow-up, or die. Study visits and specimen and data collection are to continue unchanged even in the event that a patient is withdrawn from blinded study components, or the treatment arm is unblinded, or the patient is found ineligible after randomization. The only change in this case will be how and what red cell units are prepared and issued for transfusions. See 2.2.

SECTION 5 -- STUDY VISITS AND PROCEDURES

2.5.1 OVERVIEW

There are two types of study visits: quarterly clinical visits and transfusion associated visits. Both types can occur simultaneously; for example, the first transfusion may be on the same day as the baseline clinical visit, or a weekly post transfusion blood draw for the second transfusion episode may be on the same day as the 3 month quarterly visit.

The quarterly visits should ordinarily occur every three months and are called visits 00, 03, 06, 09, 12, and so on. Visit 00 is also called the baseline visit. All forms associated with a visit are given the same visit number. For example, say an ophthalmologic exam occurs three weeks after the rest of Visit 06 is completed, and the results are not available for another three weeks. Even though six weeks have passed, when the results are recorded on Form 25, the visit number should be 06.

Many times, the forms will ask for the occurrence of events "since the last quarterly visit." The intent is to reconstruct a seamless history, with no overlap of reporting periods and no gaps between reporting periods.

Blood tests are scheduled for each VATS quarterly visit. Blood draws are required at every visit for tests to be performed locally and at the VATS central lab (Irwin Memorial Blood Bank). Central lab blood draws are identical for every VATS visit, and a CBC with platelets and WBC with differential are to be drawn and sent locally at each quarterly visit. Local laboratory results are to be abstracted by VATS clinical staff onto Form 9 (baseline) and 27 (quarterly). Whenever both local and central lab specimens are due, the central specimens have priority and should be drawn first.

Some processing of blood collected for the central lab is required prior to freezer storage. Sites should make every effort to assure that central lab specimens are processed and frozen within 4 hours of collection. Periodically results of tests performed at the central lab will be transferred electronically to the coordinating center (NERI) from the Central Laboratory.

Complete descriptions and instructions for central laboratory specimen collection, processing, storage, shipment and testing are located in the Central Laboratory Procedures portion of this manual. A schedule of testing is also located in Sections 8 and 9 of the protocol.

The transfusion associated visits will be numbered internally at NERI; clinical site staff are not required to assign visit numbers for these visits. However, the clinical coordinators will have to keep track of the first two "transfusion episodes" (see protocol section 7.1), since blood draws are required pre-transfusion and weekly for four weeks after the start of each of the first two episodes, but not at subsequent transfusions. It is possible that one of the blood draws associated with the second transfusion episode occurs on the same day as a quarterly visit.

Dilated direct and indirect ophthalmologic exams are due at baseline and every 6 months during the VATS. Efforts should be made to have these exams performed $\pm$ 3 weeks of visits 00, 06, 12, 18, etc. CMV related results are to be abstracted onto forms 7 (baseline) and 25 (quarterly).

2.5.2 CLINICAL VISITS

Procedures, visit sequence and windows are described fully for screening, enrollment, baseline and quarterly clinical visits in sections 8 and 9 of the protocol. Clinical coordinators will be provided with calendar and individual patient visit windows for clinical visits. These will not include windows for the weekly post transfusion blood draws. In order to meet VATS study objectives, it is important to adhere to the pre-transfusion data and specimen collection requirements at entry/baseline and transfusion episode two as outlined in these protocol sections. If there are any questions about conducting quarterly study visits outside of these windows, VATS staff should call NERI. If data or specimen collection outside of the established windows cannot be avoided, especially at baseline or transfusion visits, the clinical coordinator needs to notify/consult with the VATS project coordinator at NERI.

2.5.3 TRANSFUSION ASSOCIATED VISITS

In addition to sections 8 and 9 of the protocol, transfusion service procedures, transfusion related time interval requirements (windows) and sequence of activities can be found in sections 5 and 7 of the protocol. It is likely that the first transfusion episode will begin on the same day as randomization, and should begin no later than 72 hours after randomization. However, if the baseline transfusion does occur more than 72 hours after randomization, then the Coordinators should follow the procedure outlined in Communications Memorandum # 5. Pre and post transfusion associated blood draws are required at day 0 (within the 72 hours prior to beginning transfusion) and at days 7, 14, 21 and 28 post transfusion for the first two transfusion episodes (defined at protocol section 7.1) for each VATS participant.

If VATS staff miss the pre-transfusion blood draw at the 2nd Transfusion Episode, the post-transfusion weekly draws are not to be collected. Pre and post transfusion blood draws are to be postponed until the 3rd Transfusion Episode (if it occurs). In this case, the coordinator should note that the pre-transfusion draw was missed on Form 41, and forward it to NERI with the Transfusion Monitoring Form 43 corresponding to the second episode.

2.5.3.1 REQUIREMENTS FOR ALL VATS STUDY COMPONENTS TRANSFUSED

The following are required for all VATS study components transfused:

Donor Specimens

a) Red Cells: from the original collection (pre-leukoreduced for applicable units) bag and the issue (blinded study or unblinded) bag for each Red Cell unit issued to a VATS participant.

b) Platelets: from each apheresis unit or pool of platelets at issue only

Data Collection Red Cells and Platelet Transfusions

a) Donor Specimen Form 42

b) Transfusion Monitoring Form 43

c) Transfusion Event Form 44 as needed

2.5.3.2 ADDITIONAL REQUIREMENTS FOR FIRST TWO TRANSFUSION EPISODES

In addition to the above, for the first two transfusion episodes:

Specimens
a) Central Lab blood draws pre-transfusion, weeks 1, 2, 3 and 4 post transfusion

Data Collection
a) Phlebotomy Form 41 for each draw.

2.5.3.3 OVERLAPPING TRANSFUSION RELATED AND BASELINE OR QUARTERLY BLOOD DRAWS

At the baseline visit, one "set," i.e., 1 lavender top, 1 yellow top and 1 red top tube (7 ml each) of central laboratory specimens, collected prior to beginning the enrollment related transfusion, will double as the pre-transfusion and baseline visit central lab blood draw. Local labs scheduled for the baseline visit are also to be collected pre-transfusion. At baseline, the central specimens/tubes should be drawn 1st, followed by local blood tubes.

After baseline (00 visit), when pre or post transfusion related blood draws overlap with a VATS quarterly visit (03 and up), phlebotomists should attempt to collect two "sets" of central laboratory specimens, as well as the lavender tube for local complete blood count with platelets and WBC differential. A separate Phlebotomy Form 41 is to be completed for each central lab "set;" one designated as the appropriate pre or post transfusion visit and the second with the associated quarterly visit number. The blood draw in this case is to be performed in the following order of priority:

Priority	Tube Type	Volume	Destination
1	lavender top (EDTA) tube	7 ml	Central Lab (transfusion related specimens)
2	yellow top (ACD) tube	7 ml	
3	red top (clot) tube	7 ml	
4	lavender top (EDTA) tube	site specific	Local Lab (Quarterly visit tests)
5	lavender top (EDTA) tube	7 ml	Central Lab (Quarterly visit specimens)
6	yellow top (ACD) tube	7 ml	
7	red top (clot) tube	7ml	

2.5.3.4 OVERLAPPING PRE- AND POST- TRANSFUSION CENTRAL LAB BLOOD DRAWS

If pre and/or post transfusion central lab blood draws overlap, draw one "set" of central labs and label/process as the associated *second* transfusion episode(i.e., pre or 7 day post, etc.). Cancel any remaining post transfusion blood draws from the first transfusion episode. For example, say a VATS patient's second transfusion episode begins 20 days after the enrollment, or first, transfusion episode begins. The 21 and 28 day central lab blood draws from the first episode are canceled, the pre-second transfusion blood draw is to be performed, and the day 7, 14, 21 and 28 day post second transfusion draws are to be scheduled and drawn when due.

2.5.3.5 OFF-SITE TRANSFUSIONS

All efforts should be made to avoid VATS patients' receipt of transfusions at institutions or clinics not associated with the VATS study. However, if patients should receive transfusions elsewhere, VATS staff should follow these guidelines:

- If known in advance, transport the appropriate study component to the outside institution if possible.
- If it is not possible to transport the study component, arrange for patient to get appropriate treatment arm.
- Try to avoid unblinding; otherwise provide treatment arm information to a minimum number of people, e.g., on a "need to know" only basis.
- Obtain medical records and abstract information onto a Transfusion Monitoring Form if either a red cell or platelet product. Otherwise, transfusion center to note the product patient received on the weekly summary of activity sheet.
- If not known in advance, clinical coordinators should obtain as much information as possible from the patient and ideally obtain a medical record release to obtain and abstract transfusion related records from the outside institution.

2.5.3.6 PROTOCOL VIOLATIONS

NERI should be notified immediately by phone of significant protocol violations such as treatment arm errors or enrollment of patients found to be ineligible after randomization. Please note that:

- A Protocol Violation Report (Form 49) must be completed for all protocol violations.
- No Protocol Violation warrants the deactivation of a patient.
- Please refer to Communications Memorandum #5 for guidelines regarding the following Protocol Violation conditions:

  Time from Randomization to Transfusion > 72 hours.

  Patients retrospectively found to be ineligible.

  Patients retrospectively found to be ineligible because they are CMV sero-negative.

SECTION 6 -- VATS DATA COLLECTION FORMS

2.6.1 OVERVIEW

Clinically related forms and quality of life instruments are separated into "Baseline" and "Quarterly" forms. Generic central lab phlebotomy and transfusion related forms will be used throughout the study. All other data collection forms are considered "prn" or as needed forms, completed only when specific participant related situations occur that require reporting. Some of these forms are administrative in nature, such as the "Missed or Partial Visit" form, which notifies the coordinating center not to expect data forms for a particular visit. Others are to report a change in patient status, such as the "Deactivation" from study form or "Death Report" form. There are also "worksheets" which, with the exception of the "Weekly Summary of Activity", are provided as a tool for optional local use.

Detailed information, including procedural, on how and what information to record on these forms is provided in corresponding question by question specifications (QxQ's) in Chapter 5 of this manual.

VATS staff should review the QXQ corresponding to the forms he/she will be responsible for completing during the course of the study in advance of beginning, and as needed. Should situations arise that are not addressed by the QXQ's or accommodated on the form, you are encouraged to call the VATS data manager or project coordinator at NERI to report it and determine how to record the information.

We have likely anticipated a number of potential situations in designing the forms, but certainly not all of them, so please do not hesitate to notify the coordinating center of any problems with recording information requested.

Comments and explanations can also be written on the forms as needed.

A complete list of VATS data collection forms and a visit schedule appear in section 2.6.2 on the following pages.

2.6.2 VATS DATA COLLECTION FORMS AND VISIT SCHEDULE

Form 1 - Clinic Screening/Randomization

Form 2 - Blood Bank Randomization

Form 3 - Baseline Medical History

Form 4 - Baseline CMV History Medical Record Abstraction

Form 5 - Baseline Medication History

Form 6 - Baseline Abbreviated Physical Exam

Form 7 - Baseline Ophthalmologic Exam Report

Form 8 - Baseline Quality of Life

Form 9 - Baseline Local Lab Results

Form 21 - Quarterly Medical History

Form 22 - Quarterly Medical Record Abstraction

Form 23 - Quarterly Medication History

Form 24 - Quarterly Abbreviated Physical Exam

Form 25 - Quarterly Ophthalmologic Exam Report

Form 26 - Quarterly Quality of Life

Form 27 - Quarterly Local Lab Results

Form 41 - Phlebotomy Form

Form 42 - Donor Specimen Processing

Form 43 - Transfusion Monitoring

Form 44 - Adverse Transfusion Event

Form 45 - Unblinding/Withdrawal From Study Components

Form 46 - Missed/Partial Visit Report

Form 47 - Deactivation/Off-Study

Form 48 - Death Report

Form 49 - Protocol Violation Report

Form W1 - Weekly Summary of Activity

Form W2 - Segment Worksheet

Form W3 - Mail Log

FORM VISIT SCHEDULE

Form #	Title	CLINICAL FORMS			TRANSFUSION FORMS					
		Screening	Baseline/ Entry	Quarterly	T1 & T2[3]					T3 & up
				Month (±1) (03, 06, 09, 12, 15,18, 21, 24)	DAY 0	DAY 7	DAY 14	DAY 21	DAY 28	
						±1	± 2 (Days)			
1	Clinic Screening/Randomization	X								
2	Blood Bank Randomization		X							
3	Baseline Medical History		X							
4	Baseline CMV History Medical Record Abstraction		X[1]							
5	Baseline Medication History		X							
6	Baseline Abbreviated Physical Exam		X							
7	Baseline Ophthalmologic Exam Report		X							
8	Baseline Quality of Life		X							
9	Baseline Local Lab Results		X							
21	Quarterly Medical History			X						
22	Quarterly Medical Record Abstraction			X[1]						
23	Quarterly Medication History			X						
24	Quarterly Abbreviated Physical Exam			X						
25	Quarterly Ophthalmologic Exam Report			X						
26	Quarterly Quality of Life			X						
27	Quarterly Local Lab Results			X						
41	Phlebotomy Form			X	X[2]	X	X	X	X	
42	Donor Specimen Processing				X					X
43	Transfusion Monitoring				X					X
44	Adverse Transfusion Event (WHEN APPLICABLE)				(X)					(X)
	OTHER AS NEEDED FORMS: THESE FORMS ARE NOT SCHEDULED, BUT ARE USED AS NEEDED									
45	Unblinding/Withdrawal From Study Components									
46	Missed/Partial Visit Report									
47	Deactivation/Off-Study									
48	Death Report									
49	Protocol Violation Report									

NOTES

1 Due if indicated by medical history

2 Pre-transfusion; doubles as baseline Central Lab Draw

3 T1, T2, T3 = Transfusion Episodes 1, 2, 3 and up

2.6.3 BASELINE FORM OVERVIEW

2.6.3.1 CLINIC SCREENING/RANDOMIZATION FORM -- FORM 1

Form 1 doubles as a baseline eligibility checklist and as a registry/screening test. All patients considered for the VATS who are HIV positive and have had no prior transfusion should be recorded on a Form 1, even if it is obvious at the outset that the patient will not be eligible for other reasons. Similarly, if a patient is thought to be eligible but is found to be ineligible, or stratification information is not available, or the patient does not give consent, complete Form 1 and send it to NERI. In these situations, if the patient was not randomized and a VATS ID label was used on Form 1, this same VATS ID should be used for the next eligible patient. Accounting for all patients considered will allow an assessment of how representative the study sample is of the clinic population, and will be used to assess major reasons for exclusion.

For ineligible patients, check the key criteria rendering the patient ineligible. Also, at the minimum check the following questions: B1-B5, B11a and B15. If the information is available, remaining eligibility questions should also be checked.

2.6.3.2 BLOOD BANK RANDOMIZATION FORM -- FORM 2

Form 2 serves as the Clinical Coordinator's means of notifying the Transfusion Service/Blood Bank each time a patient is enrolled and successfully randomized. The Transfusion Service is to use the 5 digit randomization code written by the clinical coordinator on this form to determine the patient's treatment arm. A randomization table of treatment arm allocations by randomization code will be supplied by the coordinating center and sent directly to each site's Transfusion Coordinator at the time of study implementation. Form 2 is one of the two VATS study forms that will be provided in 3 parts. In order to keep the clinical coordinator blinded, this form is to be sent to NERI directly from the Transfusion Service/Blood Bank.

2.6.3.3 BASELINE MEDICAL HISTORY -- FORM 3

Information requested in this form may be obtained through participant interview, medical record review, or both. The medical history requested is limited to treatments or diagnoses related to VATS objectives and study endpoints involving HIV related events and virologic measures.

2.6.3.4 BASELINE CMV HISTORY MEDICAL RECORD ABSTRACTION -- FORM 4

Since new or progression of CMV end organ disease is an important study endpoint, an accurate baseline CMV history is essential. This form requires medical record review or contact with a patient's primary physician and is only completed if the patient self-reports a history of CMV disease, or if the history is suggestive of CMV, on the Medical History Form 3.

Note: This form should not be completed or submitted if the patient’s CMV history is indicated as negative on Form 3.

2.6.3.5 BASELINE MEDICATION HISTORY FORM -- FORM 5

Information requested in this form may be obtained through participant interview, medical record review, or both. We are primarily interested in medicines taken in the past month, i.e., 30 days prior to the participant's VATS enrollment visit. For some medications, we are asking the dates started and ended, as well as the specific drug name. For others, we are only interested in a "yes" or "no" response.

2.6.3.6 BASELINE ABBREVIATED PHYSICAL EXAM FORM -- FORM 6

The VATS does not require a complete physical exam. Baseline height, weight, recent history of CMV related eye symptoms and the enrollment Karnofsky score are all that are required.

2.6.3.7 BASELINE OPHTHALMOLOGIC EXAM REPORT -- FORM 7

All participants are required to have a direct and indirect dilated eye exam performed by an experienced ophthalmologist within the three weeks prior to or following enrollment. Results of the retinal exam are to be obtained, reviewed and recorded on this form by the VATS Clinical Coordinator or his/her designate. This form is not intended to be used by the ophthalmologist for recording results of an entire direct and indirect dilated exam.

2.6.3.8 BASELINE QUALITY OF LIFE FORM -- FORM 8

Most of the questions on this form are from two tested Quality of Life Instruments tailored to patients with HIV.

Ideally, this form should be self-administered by the patient (except for Section A). However, it may be necessary to read the questions to the patient, for example if administered over the phone. If the patient asks questions about items, try to help without leading the patient toward giving any particular response.

A Spanish translation of the instruments used in this form is also available, and should be provided to participants who are more comfortable with or who primarily speak and/or read Spanish.

2.6.3.9 BASELINE LOCAL LAB RESULTS -- FORM 9

Selected results of the complete blood count, platelet count, and WBC differential, performed at your local laboratory, are to be transcribed onto this form. If these tests were performed within 72 hours prior to enrollment, results may be abstracted as the baseline tests. Otherwise, specimens must be drawn and sent at enrollment and prior to the first transfusion, with results transcribed onto this form once received from the lab. Follow your local institution's requirements for requisitions, the type of blood tube or tubes and volumes required for these tests.

2.6.4 QUARTERLY FORM OVERVIEW

2.6.4.1 QUARTERLY MEDICAL HISTORY -- FORM 21

This form is the same as the baseline form except: 1) the interval is since the last quarterly visit, 2) only VATS "serious HIV related complications" are asked about, and 3) we ask about hospitalizations since the last visit.

2.6.4.2 QUARTERLY MEDICAL RECORD ABSTRACTION FORM -- FORM 22

This form is only required if: 1) patients answer "yes" or "don't know" on Form 21 to the occurrence or diagnosis of any of the VATS defined "serious HIV related complications" since the last visit, OR if any diagnosis of these complications is documented in hospital or outpatient records reviewed by the study coordinator, or is confirmed through another reliable source, such as discussions with the patient's primary M.D.

2.6.4.3 QUARTERLY MEDICATION HISTORY FORM -- FORM 23

Information requested in this form may be obtained through participant interview, medical record review, or both. We are interested in medicines taken since the last VATS Quarterly Visit. At Visit 03, "the last quarterly visit" pertains to the enrollment visit 00. For some medications, we are asking the dates started and ended, as well as the specific drug name. For others, we are only interested in a "yes" or "no" response.

2.6.4.4 QUARTERLY ABBREVIATED PHYSICAL EXAM -- FORM 24

This form is the same as the baseline form, minus a height measurement. If a visit is done by phone, patients should be asked for a recent weight (within a week) or to weigh themselves on a home scale if available. Patients are also to be queried about CMV related eye symptoms since the last visit.

2.6.4.5 QUARTERLY OPHTHALMOLOGIC EXAM REPORT -- FORM 25

This form is to be completed for all participants at every follow-up quarterly visit. Results of the VATS required eye exams at 06, 12, 18, etc. are to be abstracted onto this form, once available. Although the exam may not be performed for a few weeks after the VATS quarterly visit, record the visit number that the exam was due. Ascertain through medical record review and/or self report, whether the participant has had any other eye exams since his/her last quarterly visit. This includes exams resulting from previous referrals or from symptomatic out-patient/in-patient visits occurring since the last quarterly visit and unrelated to the VATS study. Attempts should be made to obtain, and review and record results of, all eye exams performed while a participant continues in the VATS. It is assumed that one Form 25 can accommodate a summary of all exams performed between visits. Space for up to four exam dates is available for noting new CMV disease diagnoses and/or progression requiring changes in therapy in either or both eyes. If for some reason, this is not sufficient, an additional form 25 should be completed and attached.

2.6.4.6 QUARTERLY QUALITY OF LIFE QUESTIONNAIRE -- FORM 26

The content is identical to the baseline form. In the case of a phone visit, questions should be read to the patient: either in English from the English version or in Spanish from the Spanish version of Form 26. When reading questions to a patient, care should be taken to repeat introductions and response scale descriptions in the more lengthy questions.

2.6.4.7 QUARTERLY LOCAL LAB RESULTS -- FORM 27

Selected results of the complete blood count, platelet count and WBC differential performed at your local laboratory, are to be transcribed onto this form. Follow your local institution's requirements for requisitions, the type of blood tube or tubes and volumes required for these tests.

2.6.5 -- OTHER MISCELLANEOUS FORMS OVERVIEW

2.6.5.1 PHLEBOTOMY FORM -- FORM 41

This form is being used to collect information needed to track Central Laboratory specimen identification, availability, integrity (for some tests) and storage locations (accessibility for testing). For example, since the reliability of some central lab test results will be linked to the time interval between the draw and the lab's receipt and freezing of specimens, it is very important that these be recorded on this form by both the phlebotomist and laboratory technician. The laboratory technician(s) processing VATS specimens and completing this form will need to review, and be familiar with, the Central Laboratory Procedures portion of this manual, which includes additional information needed to complete this form.

2.6.5.2 DONOR SPECIMEN PROCESSING INFORMATION FORM -- FORM 42

This form is being used to track the collection of unit (donor and/or issue) information and specimens for every Red Cell and Platelet unit issued to a VATS participant. This form may be completed at different points or by more than one person depending, for example, on whether blood products are obtained from outside suppliers. Specimens from both the donor bag (1.0 ml. segment) and the study issue bag (1 ml. aliquot) are to be collected and frozen. Locations within freezer boxes, to facilitate specimen identification for Central Lab tests, will also be tracked by this form. VATS staff responsible for completing this form will need to read, and be familiar with, the Central Laboratory Procedures portion of this manual (Chapter 4) regarding processing, storage and shipment of these specimens.

2.6.5.3 TRANSFUSION MONITORING FORM -- FORM 43

This form is to be completed for every Red Blood Cell and Platelet transfusion a participant has for the duration of the VATS study. This includes transfusion of blinded Red Cell study components, open label leukoreduced Red Cells and/or platelets received as part of the VATS study, as well as Red Cell and/or Platelet transfusions the participant reports having received elsewhere. In this case, VATS staff should obtain a medical record release and attempt to obtain transfusion related records from the outside institution's blood bank/transfusion service and medical records department.

2.6.5.4 ADVERSE TRANSFUSION EVENT -- FORM 44

This form is filled out by the Clinical Coordinator if the patient experiences an adverse transfusion reaction(s) during or within 30 minutes following a transfusion episode. It is only filled out if a transfusion reaction(s) as enumerated in Section D (D2 - D10) of the Transfusion Monitoring Form (Form 43) occurred and/or if Section G (G4) of Form 43 is checked off. Once it has been determined that an adverse transfusion reaction(s) did occur, it must be recorded on this form in Section(s) B and/or C. Unlike any other VATS form, this form is cumulative and not considered complete or sent to NERI until the specified criteria for Transfusion Physician review are met (see protocol section 7.7) or until a patient's study participation ends. Complete instructions are listed on the form and its corresponding QxQ to guide in completing this form.

2.6.5.5 UNBLINDING/WITHDRAWAL FROM STUDY COMPONENTS -- FORM 45

Use this form if the patient is withdrawn from study components and/or if the treatment arm is intentionally or unintentionally unblinded for any reason. Note that it is possible to withdraw from study components without unblinding and it is possible to unblind without withdrawing from study components. To assure effective communication of this information across study staff, the Transfusion Physician, Clinical and Transfusion coordinators must sign this form, acknowledging the patient's change in treatment status, prior to sending it to NERI.

2.6.5.6 MISSED/PARTIAL VISIT REPORT -- FORM 46

This form is used if any forms due at the baseline or at a quarterly visit are going to be missing, or if a patient completely misses a quarterly visit. Note that it is acceptable to conduct all or part of a visit by phone, (although the phlebotomy would not be completed). One exception is that the Phlebotomy Form 41 must be completed if phlebotomy is not done for a partial visit .

2.6.5.7 DEACTIVATION/OFF-STUDY FORM -- FORM 47

Use this form if the patient is being deactivated off-study, e.g., is being withdrawn from the VATS for any reason. Note that removal from study components and/or unblinding the patient is not a reason for going off-study. See protocol Section 7.2. In addition, missed visits do not constitute deactivation. Every attempt should be made to collect whatever data is available. This might involve searching medical records or corresponding with physicians, even in the absence of contact with the patient.

2.6.5.8 DEATH REPORT -- FORM 48

Use this form to report the death of a patient and assess if directly related to HIV related complications and/or transfusion event. Similar to Form 22 (QUARTERLY MEDICAL RECORD ABSTRACTION FORM) review the patient's medical records, checking for the occurrence of any of the VATS defined "serious HIV related complications" since the patient was last seen for a VATS study visit until the time of their death.

2.6.5.9 PROTOCOL VIOLATION REPORT -- FORM 49

Report any protocol violation on this form.

2.6.6 WORKSHEETS OVERVIEW

2.6.6.1 WEEKLY SUMMARY OF ACTIVITY WORKSHEET (TRANSFUSION CENTER) -- FORM W-1

This form was created to serve as: 1) a chronological record of all VATS associated units issued by each site's Blood Bank/Transfusion Center and 2) a randomization/treatment arm quality control document for the VATS transfusion coordinator and the medical coordinating center (NERI). Transfusion centers/blood banks may choose to recreate a computer version of this form, mailing a weekly printout, versus the hand-written log, to NERI. We are tracking activity by the week, i.e., Monday through Sunday. Each Monday a new log sheet should be started.

2.6.6.2 SEGMENT WORKSHEET -- FORM W-2

This form is provided for optional use by VATS transfusion centers in requesting VATS donor unit segments from outside blood bank suppliers. It is for internal use/site specific record keeping and does not need to be submitted to NERI for review or data entry.

2.6.6.3 MAIL LOG -- FORM W-3

This is an optional form, which can be attached to the front of each shipment that you send to NERI.

APPENDIX

VIRAL ACTIVATION TRANSFUSION STUDY (VATS)

COORDINATING CENTER

COMMUNICATIONS MEMORANDUM

 # 005

The Clinical Coordinator, Principal Investigator, Transfusion Coordinator, and other appropriate VATS staff should read and initial this memo indicating that they have read it.

Please file this memo in your VATS Communications Memoranda Log.

TO: Clinical Coordinators

FROM:

DATE: April 5, 1996

RE: Decisions from the 03/08/96 Ad-Hoc Committee Conference Call

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On March 8, 1996, an Ad-Hoc Committee conference call was held to discuss the correct procedure to follow for patients who have been randomized into VATS, but do not have a baseline transfusion within 72 hours of randomization. In addition to this issue, the committee discussed those cases when a randomized patient is retrospectively found to be ineligible.

The committee reaffirmed that the protocol should be followed as closely as possible. In particular, (1) randomized VATS patients should receive their baseline transfusion within 72 hours of randomization, and (2) all attempts should be made to ensure that patients are eligible before they are randomized. The committee also stressed that, once randomized, patients should be kept on study for the duration of VATS. Therefore, patients should not be formally re-screened or re-randomized once they are in the study. Delay of baseline transfusion beyond 72 hours of randomization and/or retrospective ineligibility are not in themselves reasons for deactivation.

The following outlines the operational procedure to use in cases when either the baseline transfusion does not occur within 72 hours and/or when the patient is retrospectively found to be ineligible. Whenever either of these situations occurs, the site needs to contact NERI immediately.

A. For the issue of the 72-hour window between randomization and transfusion, the following decisions were made:

1. If patient is screened as eligible and then randomized into VATS, but the patient does not receive the baseline transfusion within 72 hours of randomization, the site should:
   - complete all the baseline forms (Forms 1 through 9) if possible; if any baseline forms are missing, complete the Partial Missed Visit Form (Form 46)
   - complete the pre-transfusion Form 41 (whether draw was done or not done); the baseline blood draw should ideally be done
   - contact NERI immediately
   - complete Protocol Violation (Form 49) indicating that the transfusion did not occur within the 72-hour window from randomization
   - continue to schedule and complete Quarterly Visits (visit windows based on date of screening from Form 1)

2. In addition, if this patient is ever transfused, the site should follow the transfusion aspects of the protocol as closely as possible:
   - draw pre-transfusion specimens (within 72 hours of transfusion)
   - issue blood per treatment group randomized
   - conduct weekly blood draws post-transfusion, completing Form 41 in usual manner
   - complete Transfusion Monitoring Form and Donor/Specimen Form(s) in usual manner
   - complete Transfusion Monitoring Form and Donor/Specimen Form(s), to the extent possible, for any non-study transfusions which may have occurred between randomization and the baseline VATS transfusion

B. Regarding those cases in which a patient is randomized but retrospectively found to be ineligible, the site should:
   - continue to keep the patient in the study
   - draw pre-transfusion specimens (within 72 hours of transfusion)
   - issue blood per treatment group randomized
   - conduct weekly blood draws post-transfusion, completing Form 41 in usual manner
   - complete Transfusion Monitoring Form and Donor/Specimen Form(s) in usual manner
   - complete Transfusion Monitoring Form and Donor/Specimen Form(s), to the extent possible, for any non-study transfusions which may have occurred between randomization and the baseline VATS transfusion
   - contact NERI immediately
   - complete Protocol Violation (Form 49)
   - continue to schedule and complete Quarterly Visits (visit windows based on date of screening from Form 1)

One exception to (B.) above for which this is not possible due to ethical reasons is:

If patient is screened as eligible and randomized into VATS, but later found to be CMV negative, the site should:
   - continue to keep the patient in the study
   - take patient off VATS study components
   - follow local institutional guidelines for transfusion of HIV^{+} / CMV^{-} recipients
   - do not unblind to original treatment assignment
   - complete Withdrawal From Blinded Study Components (Form 45)
   - Complete Protocol Violation (Form 49)

VIRAL ACTIVATION TRANSFUSION STUDY

MEDICAL COORDINATING CENTER

COMMUNICATIONS MEMORANDUM

 # 011

The Clinical Coordinator, Transfusion Coordinator, Principal Investigator, and other appropriate VATS staff should read and initial this memo indicating that they have read it.

Please file this memo in your VATS Communications Memoranda Log.

TO: Clinical Coordinators

FROM:

DATE: December 13, 1996

RE: **How to code intravitreal injections and implants on the Medication History Form**

During the November 13, 1996 Steering Committee Meeting in Washington DC, the clinical committee determined how intravitreal injections and implants should be coded on the Medication History Forms (FM 05 & FM 23).

Drug Coding Conventions:

- Ganciclovir and foscarnet intravitreal injections should be coded as "other antivirals" (code 27) rather than being coded in the systemic category.
- Code 25 should be used only to record Ganciclovir implants.

Date Conventions:

- The intravitreal injection start date is the date of the first injection. The stop date is the date the series ends. For example, if a patient is receiving shots every other week, you do not need to record each injection. You should record the date when the patient stopped receiving them altogether, or if there is a prolonged interruption.
- The start date for an implant is the day the implant is placed and the stop date is the day before a new one is implanted. For cidofovir, the start and stop dates refer to the series of treatment, not each individual infusion.

VIRAL ACTIVATION TRANSFUSION STUDY

COORDINATING CENTER

COMMUNICATIONS MEMORANDUM

 # 012

The Clinical Coordinator, Transfusion Coordinator, Principal Investigator, and other appropriate VATS staff should read and initial this memo indicating that they have read it.

Please file this memo in your VATS Communications Memoranda Log.

TO: **Clinical Coordinators**

FROM:

DATE: December 14, 1996 **UPDATED 11/14/97**

RE: **Procedures Regarding Platelet Transfusions**

This memo is provided to clarify matters related to pooled platelet units in the VATS. **IMPORTANT**: This information is important for Transfusion Service staff. Please deliver a copy to the Transfusion Coordinator immediately. Thank you.

Selecting Units for Issue

- Ordinarily, pooled platelets should not be used. Apheresis platelet units are preferred over concentrate or pooled platelet units, even when fresher pooled units are available.
- When no apheresis unit is available, the freshest concentrate or pooled unit should be issued.

Specimen Collection

- Segments are not collected from any platelet units.
- Obtain aliquots from the issue bag (well-mixed final pooled unit), not from the individual donor units.

Data Collection (Updated 11/14/97)

There will be no revision to Form 42 to accommodate pooled platelet units.

- Complete only one Form 42 for the pooled unit.
- Clearly indicate on the upper half of the form that it was a pooled unit.
- Record the POOL number as the blood unit ID number on Forms 42 and 43, not the numbers of the individual donor units.
- Record the youngest unit date (i.e. the latest date collected) as the date unit collected (question B3). Please record the range of collection dates beside question B3.
- Indicate the total number of male and total number of female donor units that comprise the final pooled unit.
- Record the issue weight of the final pooled unit, not individual units.

Please don't hesitate to contact me if you have any further questions.

VIRAL ACTIVATION TRANSFUSION STUDY

MEDICAL COORDINATING CENTER

COMMUNICATIONS MEMORANDUM

 # 013

The Clinical Coordinator, Transfusion Coordinator, Principal Investigator, and other appropriate VATS staff should read and initial this memo indicating that they have read it.

Please file this memo in your VATS Communications Memoranda Log.

TO: Clinical Coordinators

FROM: Brooke Hinkson, Data Manager

DATE: December 13, 1996

RE: **Eye Exam Issues**

During the November 13, 1996 Steering Committee Meeting in Washington DC, VATS patients' non-compliance with receiving their required baseline eye exams was discussed. Many of these eye exams are not being conducted or are being conducted outside of the window period.

In an effort to increase eye exam compliance the Clinical Committee recommended and the Steering Committee approved that the clinical sites try the following measures:

- Offer the patients incentives, such as transportation reimbursement and/ or implement a $25 allowance for eye exams
- Provide educational materials regarding CMV Retinitis to the patients
- The clinical coordinators were encouraged to investigate whether or not they could utilize an additional Ophthalmologist's services which should make scheduling easier and therefore increase compliance
- Clinical coordinators should try to schedule the patient's eye exam the same day as their clinical visit, if possible

The Committee agreed to **extend the eye exam window** from δ 3 weeks to δ 4 weeks. This extended window will be applied to the baseline data.

VIRAL ACTIVATION TRANSFUSION STUDY

MEDICAL COORDINATING CENTER

COMMUNICATIONS MEMORANDUM

 # 023

The Clinical Coordinator, Transfusion Coordinator, Principal Investigator, and other appropriate VATS staff should read and initial this memo indicating that they have read it.

Please file this memo in your VATS Communications Memoranda Log.

TO: Clinical Coordinators

FROM:

DATE: July 24, 1998

RE : **Leukoreduction Requirement: Apheresis Platelets**

NOTE: This memorandum contains information important to the Transfusion Coordinator at your site. Please forward it immediately.

During their May 1998 meeting, members of the Transfusion Committee clarified the following:

1. Per a decision made early on in the study, apheresis platelets that are leukoreduced using an LRS machine must still be filtered before they are issued to a VATS patient**.**

2. Since Haemonetics uses in-line filtration, additional filtration is not necessary.

VIRAL ACTIVATION TRANSFUSION STUDY

MEDICAL COORDINATING CENTER

COMMUNICATIONS MEMORANDUM

 # 024

The Clinical Coordinator, Transfusion Coordinator, Principal Investigator, and other appropriate VATS staff should read and initial this memo indicating that they have read it.

Please file this memo in your VATS Communications Memoranda Log.

TO: Clinical Coordinators

FROM:

DATE: July 23, 1998

RE: Reporting Fungal Infections as VATS Events

Over the course of the study we have had several cases of fungemia, and recently an invasive fungal mucor case, reported and confirmed as events. At their meeting in May, the Clinical Committee decided that:

- fungal infections that meet other VATS criteria for bacterial infection, are to be reported as VATS events.
- for tracking purposes, fungal and bacterial infections will be combined in the VATS database. In other words, the current corresponding bacterial infection codes (on Forms 22 & 48) are to be used to report fungal infections.

As a result of these decisions:

1) If there is any possibility that eligible fungal infections were not previously reported as VATS events from your site, please conduct a retrospective review of patient records (per Steering Committee July 9, 1998 conference call request) to ensure all these diagnoses are captured. Please conduct this review and report any new events on Form 22 no later than October 15, 1998.

2) Using current Form 22 and Form 48 codes, report fungal infections as follows:

USE EXISTING:		TO REPORT:
Code 01	(Bacteremia, catheter related)	Bacteremia/ **Fungemia,** catheter related
Code 02	(Bacteremia, non-catheter related)	Bacteremia/**Fungemia**, non-catheter related
Code 22*	(Other serious bacterial infection) (normally sterile site)	Other serious bacterial/**fungal** infection (normally sterile site)

* Code 28 on page 1 of Form 48

Please Note: Currently, there are no plans to revise Forms 22 & 48.