HALT-C Trial Medication

I. Introduction

Trial medication for the HALT-C trial will be provided by Hoffmann-La Roche, Inc, (hereafter referred to as Roche). These medications are Peginterferon alfa-2a and ribavirin. The Data Coordinating Center (DCC) will monitor the dispensation and return of trial medication.

II. Roche to clinical center

A. Shipment of trial medication

1. Peginterferon alfa-2a
The trial medication will be shipped in boxes containing vials of 1 ml of Peginterferon alfa-2a. There will be four vials per box of180 μg/1 ml for the lead-in and week 20-responder phase and seven vials per box of 90 μg/1ml for the randomization phase. Boxes and vials are identified with a C-number, or lot number (a C followed by 6 digits).

2. Ribavirin
The trial medication will be supplied as 200 mg/tablet and shipped in bottles of 180 tablets, a one-month supply for patients receiving 1200 mg ribavirin. All bottles are labeled with a C-number (a C followed by 6 digits).

3. How to order trial medication from Roche
   a. Initial supply of trial medication
   The initial supply of trial medication will be sent per site request, based on the amount of space available in each pharmacy or storage area.

   b. Re-ordering supply of trial medication
   New supplies of trial medication can be ordered for new or existing patients by calling Regina Ingram at (973) 235-5047. Calls for new shipments must be made Monday through Wednesday. There will be no shipments made on Thursdays or Fridays.

B. Storage requirements

Medication will be shipped as ordered by the clinical center based on available space. The exception will be the NIDDK/LDS, which will receive one shipment for the lead in phase and one shipment for the randomized phase.

1. Peginterferon alfa-2a
   - Must be stored refrigerated at a temperature of 2-8 ^{o}C.
   - Seven day per week temperature logs must be kept on the pharmacy refrigerator in which the Peginterferon alfa-2a is kept.

2. Ribavirin
   - May be stored at 2-25^{o}C. Therefore, this medication may be refrigerated or stored at room temperature.

C. Accountability/documentation of the arrival of trial medication at the clinical center

1. Institutions with pre-existing institutional policies (UMass, SLU, MGH, UCI, VA-Long Beach, USC, UMichigan, VCU)
   The receiving pharmacy or clinical unit must document the arrival of the trial medication from Roche according to individual institutional procedure.

2. Institutions with no pre-existing policies (UCHSC, UTSW)
   Clinical centers without pre-existing pharmacy policies should follow the procedure below:
   a. When trial medication arrives, open the package and check to ensure that all vials and bottles are intact.
   b. Compare the shipment received with the packing list to ensure that it matches, including protocol name, amount, lot numbers, and quantity.
   c. Document the arrival of the medication using the Peginterferon alfa-2a and Ribavirin Arrival logs (Appendix 1). Clinical centers using this log should make copies of the one contained in this section.
   d. If there are discrepancies, contact Regina Ingram at Roche at (973) 235-5047.
   e. File the packing slip and any related materials in a binder with the arrival logs.

All logs documenting the arrival of trial medication will be monitored by the DCC during site visits, regardless of policy.

III. Clinical center pharmacy to coordinator

A. Dosage

1. Lead in Phase (W00-W24)
   All patients will be treated for 24 weeks with a combination of Peginterferon alfa-2a and ribavirin as described below.
   a. Peginterferon alfa-2a: Will be prescribed at 180 μg sc weekly except for patients who enter the trial with neutrophils between 1,000/mm^3 to 1,500/$mm^3$and Platelet Count from 50,000/mm^3 up to 75,000/$mm^{3,\ who}$ will start at 90 μg sc weekly (see page 69 of Protocol 1/20/2004 for details).
   b. Ribavirin: Will be prescribed based on weight.
      - For patients <75 kg, the dose will be 1000 mg (5 tablets) daily in 2 divided doses (400 mg in the morning and 600 mg in the evening taken with food, that is within one hour prior to eating or within 4 hours after eating).
      - For patients ≥75 kg, the dose will be 1200 mg (6 tablets) daily in 2 divided doses (600 mg BID taken with food, that is within one hour prior to eating or within 4 hours after eating).

2. Randomized Phase (M09-M48)
   a. For patients randomized to receive trial medication will be treated with Peginterferon alfa-2a 90 μg sc alone for 42 months.
   b. Patients who are week 20 responders will be treated with Peginterferon alfa-2a at a dose of 180 μg sc and ribavirin as previously described for an additional 24 weeks (up to week 48).
   c. See Section I, Dose Adjustment for further information on situations that require the modification or cessation of the trial medications.

B. Request for trial medication to be dispensed
Requests from the study coordinator to the pharmacy for trial medication dispensation will be made according to individual institutional procedure.

C. Dispensation of trial medication to coordinator
Trial medication should be dispensed at each visit. Patients should be dispensed enough trial medication to last until the next study visit.

D. Trial medication accountability/documentation

1. If the trial medication will be stored in a pharmacy prior to distribution, a log should be kept in the pharmacy to document the request for and dispensation to the appropriate patient. This log may be done according to individual institutional procedure. These logs will be monitored by the DCC during site visits.

2. For trial medication going directly to the clinical unit, use the Peginterferon alfa-2a and Ribavirin Arrival/Dispensation logs in Appendix 1. This log should be kept in a binder with any other forms required by individual institutional procedure. These logs will be monitored by the DCC during site visits. Clinical centers using this log should make copies of the one contained in this section. It is also acceptable to have an Excel file with the identical information that is kept by the coordinators.

IV. Coordinator to patient

A. Dispensation of trial medication to patient
Trial medication should be dispensed at each visit. Patient should be given enough trial medication to last until the next study visit as follows:

- For baseline (W00) through Week 24 (W24), the patient should receive a one-month supply of trial medication.
- Patients randomized to receive trial medication or Week 20 responders should receive a three month supply of trial medication plus the following:
  1. Information sheets (see Section F)
     - Vital information regarding dosage, administration, expected side effects and potential adverse events of **both** trial medications should be reviewed with the patients. In addition, the patient should be informed that all vials and bottles should be returned at each visit.
  2. Supplies
     - The patient should be given enough syringes, needles, alcohol wipes, gauze pads and bandages to last until the next study. They should also be provided with a sharps container or given instruction on how to use a standard household item (such as a milk carton) as a sharps container.
     - Patient should be instructed according to institutional and/or state policy regarding the disposal of syringes and sharps.
  3. Transportation of trial medication
     - Peginterferon alfa-2a must be kept at 2-8^{o}C. Therefore, each patient should be given a cooler with an ice pack for transportation of his or her trial medication from the clinic to home.
  4. Dispensation of first dose
     - It is recommended that the first dose of Peginterferon alfa-2a be self administered by the patient in the presence of the study coordinator or his/her representative. The first dose of ribavirin will also be taken in the presence of the study coordinator or his/her representative. At this time, the use of the patient diary may be demonstrated. The date the patient receives the first dose

of trial medication may be different than the Baseline visit date recorded on Form # 8, Baseline Visit Date.

B. Trial medication Accountability/documentation

1. Data forms
   The dispensation of trial medication will be documented and data entered on the following forms:
   a. Form 26, Peginterferon alfa-2a Accountability log
   b. Form 27, Ribavirin Accountability log

   These forms should be stored in the patient's HALT-C data form notebook.

2. Internal documentation
   a. A notation must be made in the patient's medical record that trial medication was dispensed. Document the dose(s), the fact that the patient is participating in the HALT-C trial, and the study phase and visit number.
   b. Other records and logs should be kept as needed according to standard institutional procedure.
   c. Forms 26 and 27 may be copied and stored with the patient's medical record as further documentation of trial medication dispensation.

V. Return of trial medication and supplies

A. Vials and bottles returned to the pharmacy
- The patient should be reminded at each study visit to return the vials and bottles containing trial medications. Any unused Peginterferon alfa-2a or ribavirin should also be returned.
- Once returned by the patient, and documented by the appropriate staff, the vials and bottles may be destroyed in an appropriate manner according to individual institutional procedure.
- If there are no institutional procedures, vials, bottles and tablets may be returned to Roche for destruction. See instructions at the end of this document.

B. Trial medication accountability/documentation

1. Data Forms
   The return of trial medication will be documented and data entered on the following forms:
   a. Form 26, Peginterferon alfa-2a Accountability log
   b. Form 27, Ribavirin Accountability log
   c. Form 926, Lost Drug Accountability

   These forms should be stored in the patient's HALT-C data form notebook.

2. Internal documentation
   a. Institutions with pre-existing institutional policies (UMass, SLU, MGH, UCI, VA-Long Beach, USC, UMichigan, VCU).
      - The receiving pharmacy or clinical unit must document the return and destruction of unused trial medication according to individual institutional procedure. These logs will be monitored by the DCC during site visits.
      - A copy of the individual institutional procedure for the destruction of vials must be obtained and kept with the study logs and records. This will be reviewed at annual site monitoring visits.
   b. Institutions with no pre-existing policies (UCHSC, UTSW)

- Clinical centers without pre-existing pharmacy policies should follow the procedure below:
  i. Document the return of vials and tablets on the Accountability logs, forms # 26 and # 27.
  ii. Return all vials, bottles, and tablets to Roche according Appendix 1 of this document.
  iii. Document the return of the vials, bottles and tablets on the Peginterferon alfa-2a /Ribavirin Return log found in Appendix 2. Clinical centers using this log should make copies of the one contained in this section. This log should be kept in a binder with any other forms required by individual institutional procedure. The log will be monitored by the DCC during site visits.

C. Return of sharps container
Patient should be instructed to return syringes and sharps containers according to individual institutional or state policy. Patients may also be advised that many communities have special procedures for discarding medical wastes. The local department of public works may have more information.

VI. Permanent cessation of trial medication

A. Notify pharmacy via internal procedure
When a patient comes off trial medication permanently for any reason, the pharmacy should be notified via individual institutional procedure.

B. Documentation

1. Data forms
The permanent cessation of trial medication should be documented on the following forms:
   a. Form 28, Peginterferon alfa-2a Dose Adjustment log
   b. Form 29, Ribavirin Dose Adjustment log
   c. Form 19, Early Termination of Peginterferon alfa-2a treatment
   d. Form 25, Early Termination from Trial (if appropriate)

2. Internal documentation
The cessation of trial medication should be documented in the patient's medical record and in appropriate pharmacy documents. The date of the last dose, the reason(s) for discontinuation, and any follow up required (and outcomes of the follow up) should be recorded.

VII. Quality Assurance

The following information will be monitored by the DCC during site visits:
A. Logs documenting the arrival of trial medication from Roche.
B. Logs documenting the distribution of trial medication to study coordinator.
C. Temperature logs.
D. Forms # 19, 25, 26, 27, 28, 29 (enter as needed).
E. Logs documenting the return and destruction of unused trial medication and all vials and bottles.
F. A copy of the institutional procedure for the destruction of vials.
G. A copy of the patient's medical record noting the dispensation of trial medication. Identifying patient information such as name or medical record number should be blacked out and replaced with the study ID number.

APPENDIX 1

PEGINTERFERON ALFA-2A AND RIBAVIRIN ARRIVAL LOGS AND Q X QS

HALT-C Trial

Peginterferon alfa-2a Arrival/Dispensation Log

Not to be Data Entered

Version: 06/15/00

To be maintained by the Clinical Center Study Coordinator to document the arrival of Peginterferon alfa-2a vials from Roche and the dispensation of the shipment to the patient. The shipment received should be compared to the packing slip and documented here. This should not be entered in the Trial Data Management System.

Invoice Number OR Patient Number	Lot Number	Receipts (Peginterferon alfa-2a Vials)		Dispensed (Peginterferon alfa-2a Vials)		Balance Remaining	Initials
		Date Received	Quantity Received	Date Dispensed	Quantity Dispensed		
	C-__ __ __ __ __ __	__ __/__ __/__ __ __ __	__ __ __	__ __/__ __/__ __ __ __	__ __ __	__ __ __	__ __ __
	C-__ __ __ __ __ __	__ __/__ __/__ __ __ __	__ __ __	__ __/__ __/__ __ __ __	__ __ __	__ __ __	__ __ __
	C-__ __ __ __ __ __	__ __/__ __/__ __ __ __	__ __ __	__ __/__ __/__ __ __ __	__ __ __	__ __ __	__ __ __
	C-__ __ __ __ __ __	__ __/__ __/__ __ __ __	__ __ __	__ __/__ __/__ __ __ __	__ __ __	__ __ __	__ __ __
	C-__ __ __ __ __ __	__ __/__ __/__ __ __ __	__ __ __	__ __/__ __/__ __ __ __	__ __ __	__ __ __	__ __ __
	C-__ __ __ __ __ __	__ __/__ __/__ __ __ __	__ __ __	__ __/__ __/__ __ __ __	__ __ __	__ __ __	__ __ __
	C-__ __ __ __ __ __	__ __/__ __/__ __ __ __	__ __ __	__ __/__ __/__ __ __ __	__ __ __	__ __ __	__ __ __

HALT-C Trial

Ribavirin Arrival/Dispensation Log

<u>Not to be Data Entered</u>

Version: 06/15/00

To be maintained by the Clinical Center Study Coordinator to document the arrival of Ribavirin bottles and tablets from Roche and the dispensation of the shipment to the patient. The shipment received should be compared to the packing slip and documented here. This should not be entered in the Trial Data Management System.

Invoice Number OR Patient Number	Lot Number	Receipts (Ribavirin Tablets)		Dispensed (Ribavirin Tablets)		Balance Remaining	Initials
		Date Received	Quantity Received	Date Dispensed	Quantity Dispensed		
	C-__ __ __ __ __ __	__ __/__ __/__ __ __ __	__ __ __	__ __/__ __/__ __ __ __	__ __ __	__ __ __	__ __ __
	C-__ __ __ __ __ __	__ __/__ __/__ __ __ __	__ __ __	__ __/__ __/__ __ __ __	__ __ __	__ __ __	__ __ __
	C-__ __ __ __ __ __	__ __/__ __/__ __ __ __	__ __ __	__ __/__ __/__ __ __ __	__ __ __	__ __ __	__ __ __
	C-__ __ __ __ __ __	__ __/__ __/__ __ __ __	__ __ __	__ __/__ __/__ __ __ __	__ __ __	__ __ __	__ __ __
	C-__ __ __ __ __ __	__ __/__ __/__ __ __ __	__ __ __	__ __/__ __/__ __ __ __	__ __ __	__ __ __	__ __ __
	C-__ __ __ __ __ __	__ __/__ __/__ __ __ __	__ __ __	__ __/__ __/__ __ __ __	__ __ __	__ __ __	__ __ __

HALT-C Trial

Peginterferon alfa-2a and Ribavirin Arrival/Dispensation Logs

Q x Q Version 06/15/00

Purpose of these logs: The Peginterferon alfa-2a and Ribavirin Arrival/Dispensation logs are used to document the arrival of trial medication from Roche and the subsequent distribution to the patient. These logs are to be maintained by the study coordinator or designate in clinical centers where there is no pre-existing policy or form to document the arrival of trial medication from the study sponsor. The logs should be kept together in a binder near the supply of trial medication in a room or storage space that can be locked. Access should be limited to appropriate personnel. The logs are not data entered into the trial data management system. An excel file with the identical information is also an acceptable log kept by the coordinators.

When to complete these logs: These logs should be completed for patients each time Peginterferon alfa-2a or Ribavirin arrives from Roche and/or is dispensed to the patient.

Note: These forms do not replace the Peginterferon alfa-2a and Ribavirin Accountability Logs (Forms # 26 and 27). More detailed information on the ordering, shipment and dispensation of trial medication is contained in the Trial Medication section of the Manual of Operations.

I. GENERAL INFORMATION

- Compare each shipment of trial medication received with the packing slip.
- Use a new log for each shipment.
- No information should be entered in shaded areas.
- Separate logs are kept for Peginterferon alfa-2a and Ribavirin.
- Document each receipt or dispensation of trial medication across the row.
- Enter a separate line for each arrival, dispensation, or lot number.
- When there are no more lines on the page, start a new form. Please note that the footer has space for a page number to be manually inserted.

INVOICE NUMBER OR PATIENT NUMBER

- If recording the arrival of a shipment from Roche, document the invoice number on the packing slip here.
- If recording dispensation to the patient, document the 6 digit patient ID number here. Labels provided by the DCC may also be used.

LOT NUMBER

- Document the C-number (lot number) from the Peginterferon alfa-2a vial(s) and Ribavirin bottle(s) contained in the shipment or dispensed to the patient.
- If two lot numbers are contained in a shipment or two lot numbers are dispensed to a patient, use two lines.

RECEIPTS (PEGINTERFERON ALFA-2A VIALS OR RIBAVIRIN TABLETS)

- Complete this section for shipments of trial medication received. Start a new log for each shipment

- Date Received: Document the date the shipment arrived in the month, day, and year.
- Quantity Received: Document the number of Peginterferon alfa-2a vials or tablets of Ribavirin received.
- If trial medication is being dispensed, skip this section.

DISPENSED (PEGINTERFERON ALFA-2A VIALS OR RIBAVIRIN TABLETS)

- Complete this section for trial medication dispensed to the patient.
- Date Dispensed: Document the date the medication was dispensed in the month, day, and year.
- Quantity Received: Document the number of Peginterferon alfa-2a vials or tablets of Ribavirin dispensed to the patient.
- If medication was received, skip this section.

BALANCE REMAINING

- Document the number of vials or tablets remaining in stock after each arrival or dispensation.

INITIALS

- Enter the initials of the person documenting each arrival or dispensation.
- Enter the first initial in the first space provided, middle initial in the second space provided, and the last initial in the third space provided.
- If the person does not have a middle initial, enter the first initial in the first space provided, leave the second space blank, and enter the last initial in the third space provided.
- If the person has a hyphenated last name or 2 last names, enter the initial of the first last name in the last space.

APPENDIX 2

PEGINTERFERON ALFA-2A AND RIBAVIRIN RETURN LOGS

HALT-C Trial

PEGINTERFERON ALFA-2A Return Log

Not to be Data Entered

Version: 06/15/00

To be maintained by the Clinical Center Study Coordinator to document the return and destruction of Peginterferon alfa-2a vials. This should not be entered in the Trial Data Management System.

Patient ID Number	Date Peginterferon alfa-2a Vials Returned	Lot Number	Number of Vials Returned	Date Peginterferon alfa-2a Vials Destroyed	Initials
__ __-__ __ __- __	__ __/__ __/__ __ __ __	C-__ __ __ __ __ __	___ ___ ___	__ __/__ __/__ __ __ __	___ ___ ___
__ __-__ __ __- __	__ __/__ __/__ __ __ __	C-__ __ __ __ __ __	___ ___ ___	__ __/__ __/__ __ __ __	___ ___ ___
__ __-__ __ __- __	__ __/__ __/__ __ __ __	C-__ __ __ __ __ __	___ ___ ___	__ __/__ __/__ __ __ __	___ ___ ___
__ __-__ __ __- __	__ __/__ __/__ __ __ __	C-__ __ __ __ __ __	___ ___ ___	__ __/__ __/__ __ __ __	___ ___ ___
__ __-__ __ __- __	__ __/__ __/__ __ __ __	C-__ __ __ __ __ __	___ ___ ___	__ __/__ __/__ __ __ __	___ ___ ___
__ __-__ __ __- __	__ __/__ __/__ __ __ __	C-__ __ __ __ __ __	___ ___ ___	__ __/__ __/__ __ __ __	___ ___ ___
__ __-__ __ __- __	__ __/__ __/__ __ __ __	C-__ __ __ __ __ __	___ ___ ___	__ __/__ __/__ __ __ __	___ ___ ___
__ __-__ __ __- __	__ __/__ __/__ __ __ __	C-__ __ __ __ __ __	___ ___ ___	__ __/__ __/__ __ __ __	___ ___ ___

HALT-C Trial

Ribavirin ™ Return Log

Not to be Data Entered

Version: 06/15/00

To be maintained by the Clinical Center Study Coordinator to document the return and destruction of Ribavirin tablets and bottles. This should not be entered in the Trial Data Management System. A copy of this log should be sent monthly to the DCC.

Patient ID Number	Date Ribavirin Tablets Returned	Lot Number	Number of Tablets Returned	Date Ribavirin Tablets Destroyed	Initials
__ __-__ __ __ -__	__ __/__ __/__ __ __ __	C-__ __ __ __ __ __	___ ___ ___	__ __/__ __/__ __ __ __	___ ___ ___
__ __-__ __ __ -__	__ __/__ __/__ __ __ __	C-__ __ __ __ __ __	___ ___ ___	__ __/__ __/__ __ __ __	___ ___ ___
__ __-__ __ __ -__	__ __/__ __/__ __ __ __	C-__ __ __ __ __ __	___ ___ ___	__ __/__ __/__ __ __ __	___ ___ ___
__ __-__ __ __ -__	__ __/__ __/__ __ __ __	C-__ __ __ __ __ __	___ ___ ___	__ __/__ __/__ __ __ __	___ ___ ___
__ __-__ __ __ -__	__ __/__ __/__ __ __ __	C-__ __ __ __ __ __	___ ___ ___	__ __/__ __/__ __ __ __	___ ___ ___
__ __-__ __ __ -__	__ __/__ __/__ __ __ __	C-__ __ __ __ __ __	___ ___ ___	__ __/__ __/__ __ __ __	___ ___ ___
__ __-__ __ __ -__	__ __/__ __/__ __ __ __	C-__ __ __ __ __ __	___ ___ ___	__ __/__ __/__ __ __ __	___ ___ ___

HALT-C Trial

Peginterferon alfa-2a and Ribavirin Return Logs

Q x Q Version 6/15/00

Purpose of these logs: The Peginterferon alfa-2a and Ribavirin Return logs are used to document the return of trial medication from the patient and its subsequent destruction. Patient should return all used and unused vials of Peginterferon alfa-2a and all bottles and unused tablets of Ribavirin. These logs are to be maintained by the study coordinator or designate in clinical centers where there is no pre-existing policy or form to document the arrival of trial medication from the study sponsor. The logs should be kept together in a binder near the supply of trial medication in a room or storage space that can be locked. Access should be limited to appropriate personnel. The logs are not data entered into the trial data management system. An excel file with the identical information is also an acceptable log kept by the coordinators.

When to complete these logs: These logs should be completed for patients each time Peginterferon alfa-2a or Ribavirin is returned by the patient and destroyed.

Note: These forms do not replace the Peginterferon alfa-2a and Ribavirin Accountability Logs (Forms # 26 and 27). More detailed information on the return and destruction of vials, bottles, and unused trial medication is contained in the Trial Medication section of the Manual of Operations.

II. GENERAL INFORMATION

- Separate logs are kept for Peginterferon alfa-2a and Ribavirin.
- Document each receipt or dispensation of trial medication across the row.
- Enter a separate line for each patient and/or lot number.
- When there are no more lines on the page, start a new form. Please note that the footer has space for a page number to be manually inserted.

PATIENT ID NUMBER

- Enter the 6-digit ID number for each patient returning trial medication vials or tablets. Labels provided by the DCC may be used.

DATE RETURNED (PEGINTERFERON ALFA-2A VIALS OR RIBAVIRIN TABLETS)

- Document the date the vials or tablets were returned in the month, day, and year format.

LOT NUMBER

- Document the C-number (lot number) from the Peginterferon alfa-2a vial(s) and Ribavirin bottle(s) returned by the patients(s)

NUMBER RETURNED (PEGINTERFERON ALFA-2A VIALS OR RIBAVIRIN TABLETS)

- Document the number of Peginterferon alfa-2a vials or tablets of Ribavirin returned by the patient. Do not record the number of Ribavirin bottles.

DATE PEGINTERFERON ALFA-2A DESTROYED

- Document the date the vials or tablets were returned destroyed or sent for destruction in the month, day, and year format.

INITIALS

- Enter the initials of the person documenting each arrival or dispensation.
- Enter the first initial in the first space provided, middle initial in the second space provided, and the last initial in the third space provided.
- If the person does not have a middle initial, enter the first initial in the first space provided, leave the second space blank, and enter the last initial in the third space provided.
- If the person has a hyphenated last name or 2 last names, enter the initial of the first last name in the last space.