HALT-C Randomized Phase

Patients must be assessed for eligibility to enter the Randomization Phase. There are three different ways to enter the Randomization phase:

- An Express Group patient can be enrolled directly into the Randomization Phase after eligibility is confirmed during the Screening Phase.
- A Lead-in Group patient who did not respond to the Lead-in treatment (detectable HCV-RNA at the Week 20 visit during the Lead-In Phase) is eligible for enrollment in the Randomization Phase.
- When a Responder Phase patient subsequently has detectable HCV-RNA test results, the patient is eligible to enter the Randomization phase of the trial as a Breakthrough or Relapser patient.

Patients are randomized into one of two study arms: the Control Arm and the Treatment Arm. Control Arm patients have standard follow-up visits for an additional 4 years. Treatment Arm patients have standard follow-up visits for four years with low-dose Peginterferon alfa-2a treatment for 3.5 years.

At the first visit in the Randomization Phase, the patient learns whether s/he is assigned to the Control Arm and the Treatment Arm. Study medications are dispensed to those in the Treatment Arm. There are three different types of visits to enter the Randomization phase:

- Lead-in Group patients learn Control/Treatment Arm assignment at the Week 24 (W24) visit.
- Express Group patients have a Randomization Visit (R00) directly following the Screening Phase.
- Breakthrough/Relapser patients have a Randomization Visit (R00) after having detectable HCV-RNA test results during the Responder Phase.

Assessment For Randomization

Lead-In Group Patients: Assessment For Randomization

Between Weeks 20 and 24 for Lead-in Group patients the patient is assessed in real time for eligibility, then randomized via the DMS. The following parameters must be assessed to determine eligibility for randomization:

W20 HCV RNA

HCV-RNA must be positive to be eligible for randomization. If the HCV-RNA is negative, the patient will follow the W20 Responder protocol at this time. These results will be sent directly to the clinical center via email and can be seen in the DMS under Form #31: Central Lab—HCV RNA.

W20 Ultrasound (MRI, CT)

There must be no evidence of HCC. Record the results of the Week 20 ultrasound (MRI, CT) on Form #22: Ultrasound (MRI, CT) after evaluation at the clinical center by appropriate medical personnel.

W20 lab tests

Ensure that the Week 20 lab tests performed at the local clinical center laboratories continue to meet the original eligibility criteria for the HALT-C Trial and record these results on Form #30: Local Lab. The AFP must be less than 1000 ng/ml and is recorded on Form #34: AFP.

Screening (S00) biopsy reading

Obtain central reading of Screening biopsy to determine Ishak score (2-4 indicates fibrosis; 5-6 indicates cirrhosis). This score is recorded on Form #51: Central Review of Pathology, by the Data Coordinating Center under the Screening Visit in the DMS.

Week 20 CTP score
Calculate the CTP score for Week 20 and record on Form #15.

Clinical Outcomes
If the patient has any clinical outcome s/he is not eligible for the Randomized Phase. Monitor the patient for the appearance of any outcome variable that would exclude the patient from further participation. If appropriate, complete Form #63: Clinical Outcome

Determining eligibility for randomization of Lead-in Group patients
Lead-in Group Patients are eligible for randomization to Treatment or Control Arm if the following are true:

- They have detectable HCV RNA from the week 20 visit.
- The AFP level is below 1000 ng/ml.
- There is no evidence of HCC on the ultrasound.
- The CTP score is less than 7 at Week 12 and/or Week 20.
- There is no evidence of a clinical outcome.
- The patient is willing to be randomized.
- The patient is willing to be followed for the duration of the study, regardless of assignment to Treatment or Control Arm.
- The patient is compliant with study medications and visits.

Express Group Patients: Assessment For Randomization
Express Group patients are assessed during the Screening Phase. By definition, Express Group patients bypass the Lead-in Phase. If the patient is eligible for the trial, the informed consent has been signed, and the Express Screening Checklist (Form #94) completed, and the patient is deemed eligible during the Screening Phase, the patient may be assessed for eligibility for the Randomization Phase. The following timeframes must be adhered to for the Randomization (R00) visit:

- An Express Group patient cannot be off pegylated interferon and ribavirin combination for more than 6 months.
- The pre-treatment liver biopsy must be within 18 months of the Randomization Visit (R00).

The following parameters must be assessed to determine eligibility for randomization:

Screening HCV RNA
- HCV-RNA must be positive to be eligible for randomization. (If the HCV-RNA is negative, the patient is not eligible for continuing in the HALT-C Trial.)
- These results will be sent directly to the clinical center from the central virology lab via email and can be seen in the DMS under Form #31: Central Lab—HCV RNA.

Screening Ultrasound (MRI, CT)
There must be no evidence of HCC. Record the results of the Screening Ultrasound (MRI, CT) on Form #22: Ultrasound (MRI, CT) after evaluation at the clinical center by appropriate medical personnel.

Screening lab tests
- The Screening lab tests performed at the local clinical center laboratories must meet the original eligibility criteria for the HALT-C Trial as recorded on Form #30: Local Lab, and Form #94: Express Screening Checklist.
- The AFP must be less than 1000 ng/ml and is recorded on Form #34: AFP. If an Express patient has a Screening AFP of between 200 and 1000 ng/L, an ultrasound must be normal and an MRI or CT must be normal for the patient to be eligible for enrollment.

Screening biopsy reading

- Obtain central reading of Screening biopsy to determine Ishak score (2-4 indicates fibrosis; 5-6 indicates cirrhosis).
- This biopsy for Express patients must have been performed pre-treatment and within 18 months of the Randomization Visit (R00).
- This reading is recorded on Form #51: Central Review of Pathology, by the Data Coordinating Center under the Screening Visit in the DMS.

Screening CTP scores

Calculate the CTP scores for both Screening visits and record on two separate Form #15's.

Clinical Outcomes

If the Express Group patient has any clinical outcome, s/he is not eligible for the Randomized Phase. Monitor the patient for the appearance of any outcome variable that would exclude the patient from further participation.

Determining eligibility for randomization of Express Group patients

Express Group patients are eligible for randomization to the Treatment or Control Arm if the following are true:

- There is detectable HCV-RNA at the Screening visit.
- The AFP level is below 1000 ng/ml.
- There is no evidence of HCC on the ultrasound.
- The CTP scores at Screening Visit 1 or Screening Visit 2 must be 7 or less (i.e., one can be as high as 7, the other must be less than 7)
- There is no evidence of a clinical outcome.
- The patient is willing to be randomized.
- The patient is willing to be followed for the duration of the study, regardless of assignment to Treatment or Control Arm.
- The patient is compliant with study medications and visits.

Express Group patients with any of the following are not eligible for continuation in the HALT-C protocol:

- The AFP level is equal to or above 1000 ng/ml.
- There is evidence of HCC on the ultrasound.
- Both CTP scores are 7 or greater at Screening Visit 1 and Screening Visit 2.
- There is evidence of a clinical outcome.
- The patient is unwilling to be randomized.
- The patient is unwilling to be followed for the duration of the study.
- The patient is non-compliant with medications or study visits.

Stratification

Patients are stratified into cirrhotic (Ishak fibrosis stage 5 or 6) or non-cirrhotic groups (Ishak fibrosis stage 2, 3 or 4) based on the central reading of the Screening liver biopsy.

Form #99: Randomization Checklist II.

Data collected to assess the eligibility of the Express Group patients for randomization is recorded on Form #99. This form triggers the DMS to randomize patients to the Treatment or Control Arm. *This form should only be completed and data entered if the patient is eligible and willing to be randomized.* Data enter the form in the patient's Screening visit. The Randomization Visit (R00) must be held within 2 weeks of data entering Form #99.

Form #1: Trial ID Assignment.
For those Express patients who were continuing on a course of interferon and ribavirin during the Screening Phase, go back to the questions on Form #1, regarding the number of weeks and dose adjustments for interferon and ribavirin and complete, if applicable, at this point in time.

Breakthrough/Relapser Patients: Assessment For Randomization
Responder Phase patients undergo periodic HCV-RNA testing. Breakthrough patients have a detectable HCV-RNA test during Weeks 24 to 48. Relapse patients have a detectable HCV-RNA test after Week 48. Breakthrough/Relapse patients are assessed for entry into the Randomization Phase after the confirmatory positive HCV-RNA result is received from the central virology laboratory. The following parameters must be assessed to determine eligibility for randomization:

Responder Phase HCV-RNA
- HCV-RNA must have been positive at two separate time points during the Responder Phase to be eligible for randomization. If there is no confirmatory positive HCV-RNA, the patient is not eligible for randomization. These results will be sent directly to the clinical center from the central virology lab via email and can be seen in the DMS under Form #31: Central Lab—HCV RNA and Form #37: Repeat HCV RNA.

Responder Phase Ultrasound (MRI, CT)
- An Ultrasound (MRI, CT) needs to be performed and recorded on Form #22: Ultrasound (MRI, CT) after evaluation at the clinical center by appropriate medical personnel.
- If the patient is at W36 or W60, schedule an ultrasound (all other Responder Phase visits have a scheduled Ultrasound).
- There must be no evidence of HCC.

Responder Phase Lab tests
- The AFP from the most recent Responder Phase Visit must be less than 1000 ng/ml.
- The most recent labs performed at the local clinical center laboratories from the most recent Responder Phase Visit must meet the original eligibility criteria for randomization as recorded on Form #30: Local Lab.

Responder Phase Screening (S00) biopsy reading
- Use the central reading of Screening biopsy to determine Ishak score (2-4 indicates fibrosis; 5-6 indicates cirrhosis).
- This reading is recorded on Form #51: Central Review of Pathology, by the Data Coordinating Center under the Screening Visit in the DMS.
- Patient must be willing to be re-biopsied if their Screening biopsy is greater than 30 months from the time of Breakthrough/Relapse Randomization.

Responder Phase CTP scores
Use the CTP scores from the two most recent visits during the Responder Phase.

Clinical Outcomes
If the patient has any clinical outcome s/he is not eligible for the Randomized Phase. Monitor the patient for the appearance of any outcome variable that would exclude the patient from further participation. If appropriate, Complete a Form #63: Clinical Outcome.

Determining eligibility for randomization of Breakthrough/Relapse patients
Breakthrough/Relapse patients are eligible for randomization to Treatment or Control Arm if the following are true:

- There are two detectable HCV RNA tests at two separate time points in the Responder Phase.
- The AFP level is below 1000 ng/ml.
- There is no evidence of HCC on the ultrasound.
- The Screening biopsy is less than 30 months from the time of Breakthrough/Relapse Randomization or a repeat biopsy is performed at the site and read by the Central Pathology for stratification of Randomization.
- The CTP score is 7 or less at the two most recent Responder Phase visits.
- There is no evidence of a clinical outcome.
- The patient is willing to be randomized.
- The patient is willing to be followed for the duration of the study, regardless of assignment the Treatment or Control Arm.
- The patient is compliant with study medications and visits.

If the Breakthrough/Relapse patient is not eligible and/or not willing to be randomized, schedule the next Responder Phase visit. Breakthrough/Relapse Patients with any of the following are not eligible for randomization:

- The AFP level is equal to or above 1000 ng/ml.
- There is evidence of HCC on the ultrasound.
- The patient is unwilling to repeat a biopsy, if the Screening biopsy is greater than 30 months from time of Breakthrough/Relapse Randomization.
- Both CTP scores are 7 or greater at the two most recent Responder Phase visits.
- There is evidence of a clinical outcome.
- The patient is unwilling to be randomized.
- The patient is unwilling to be followed for the duration of the study.
- The patient is non-compliant with medications or study visits.

Stratification

Breakthrough/Relapse patients are stratified into cirrhotic (Ishak fibrosis stage 5 or 6) or non-cirrhotic groups (Ishak fibrosis stage 2, 3, or 4) based on the central reading of the Screening liver biopsy (Form #51). In the case of Screening biopsy that is greater than 30 months from time of Breakthrough/Relapse Randomization, the patient is stratified based on the central reading of the most recent biopsy (Form #51).

Form #99: Randomization Checklist II.

Data collected to assess the eligibility of the Breakthrough/Relapse patients for randomization is recorded on Form #99. This form triggers the DMS to randomize patients to the Treatment or Control Arm. *This form should only be completed and data entered if the patient is eligible and willing to be randomized.* This form is added to the patient's record by selecting the menu item "randomize responders" under "Reports/Patient Visit Related".

Randomization Visit

Lead-In Group Patients: Week 24 (W24) Randomization Visit
At the Week 24 study visit, patients randomized to the Treatment Arm will receive the appropriate dose of Peginterferon alfa-2a 90 μg and discontinue the ribavirin. Patients randomized to in the Control Arm will discontinue all study medications. Required testing and interviews are:

W24 Patient administered questionnaires
- Alcohol use (Form #42)

W24 Interviews
- Study visit (Form #10)
- Medications Interview (Form #12)

W24 Tests
- Endoscopy (Form #23). The endoscopy must be performed within 4 weeks of Week 24 for those patients being randomized who have not had an endoscopy in the previous 12 months. Responders will not have an endoscopy performed at this time.

W24 Local lab tests (Form #30)
- Liver chemistries (AST, ALT, alkaline phosphatase, total bilirubin, albumin, and globulin [or total protein])
- Complete blood count with diff (WBC, neutrophils, hematocrit, hemoglobin, platelets
- TSH
- Pregnancy test (for women of child bearing potential)

W24 Central lab tests (Forms #31 and #72)
- HCV-RNA (sent to central repository for shipping for the central virology lab. This specimen will be sent to the repository but not tested and reported until later in the study.

W24 Forms
- Form #10: Study Visit
- Form #12: Medications Interview
- Form #23: Endoscopy (if applicable)
- Form #26: Peginterferon Accountability Log
- Form #27: Ribavirin Accountability Log
- Form #28: Peginterferon Dose Adjustment Log
- Form #29: Ribavirin Dose Adjustment Log
- Form #30: Local Lab
- Form #31: Central Lab—HCV-RNA (tested and reported later in the study)
- Form #42: Alcohol Use
- Form #72: Lead in Phase Aliquot Form
- Form #110: Central Endoscopy (completed by Central Endoscopy Committee and data entered at DCC)

W24 Instructions to Treatment Arm Patients
- Collect all vials of Peginterferon alfa-2a 180 μg and record return on Form #26: Peginterferon Accountability Log.
- Collect all ribavirin and record return on Form #27: Ribavirin Accountability Log.
- Dispense trial medications. Patients will receive Peginterferon alfa-2a 90 μg sc weekly in the Randomized Phase. Record dispensation of Peginterferon on Form #26: Peginterferon

Accountability Log. (If the patient was taking 45 μg at the time of randomization to treatment, s/he may remain on that dose.)
- Give medication instructions and follow up information regarding Study Visit Month 9.
- Record Peginterferon dose adjustment on Form #28: Peginterferon Dose Adjustment.
- Record ribavirin dose discontinuation on Form #29: Ribavirin Dose Adjustment.
- Notify pharmacy of patient assignment.

W24 Instructions to Control Arm Patients
- Collect all vials of Peginterferon alfa-2a 180 μg and record return on Form #26: Peginterferon Accountability Log.
- Collect all ribavirin and record return on Form #27: Ribavirin Accountability Log.
- Give follow up information regarding Study Visit Month 9.
- Record Peginterferon dose discontinuation on Form #28: Peginterferon Dose Adjustment.
- Record ribavirin dose discontinuation on Form #29: Ribavirin Dose Adjustment.
- Notify pharmacy of patient assignment.

Express Group Patients: Randomization Visit (R00)
The R00 visit is the first visit of the Randomization Phase for the Express Group patients in the Treatment or Control Arm of the trial. Those in the Treatment Arm will receive the appropriate dose of Peginterferon alfa-2a (90 μg). Those in the Control Arm will not receive any study medications. Required testing and interviews are:

R00 Express Patient administered questionnaires
- Alcohol use (Form #42)
- Symptoms (Form #43)
- Physical Activity (Form #140)
- Analgesics Medications History (Form #141)

R00 Express Interviews
- Medications Interview (Form #7)
- Life Events Status (Form #45)

R00 Express Tests
- Endoscopy (Form #23). The endoscopy must be performed within 4 weeks of the Randomization Visit (R00) for those patients being randomized.

R00 Express Local lab tests (Form #30)
- Liver chemistries (AST, ALT, alkaline phosphatase, total bilirubin, albumin, and globulin [or total protein])
- Complete blood count with diff (WBC, neutrophils, hematocrit, hemoglobin, platelets
- TSH
- Pregnancy test (for women of child bearing potential)

R00 Express Central lab tests (Form #31)
- HCV-RNA (sent to central repository for shipping for the central virology lab. This specimen will be sent to the repository but not tested and reported until later in the study.

R00 Express Forms
- Form #7: Medications Interview
- Form #15: CTP
- Form #23: Endoscopy

- Form #26: Peginterferon Accountability Log
- Form #30: Local Lab
- Form #31: Central Lab—HCV-RNA (tested and reported later in the study)
- Form #34: AFP
- Form #42: Alcohol Use
- Form #43: Symptoms
- Form #45: Life Events Status
- Form #77: Randomization Visit (R00) Aliquot Form
- Form #98: Randomization Visit (Data enter first)
- Form #110: Central Endoscopy (completed by Central Endoscopy Committee and data entered at DCC)
- Form #140: Physical Activity
- Form #141: Analgesics Medications History

R00 Express Instructions to Treatment Arm Patients

- Dispense trial medications and record on Form#26: Peginterferon Accountability Log. Patients will receive Peginterferon alfa-2a 90 μg sc weekly in the Randomized Phase.
- Give medication instructions and follow up information regarding Study Visit Month 9.
- Notify pharmacy of patient assignment.

R00 Express Instructions to Control Arm Patients

- Patients will NOT receive any trial medications in the Randomized Phase.
- Give follow up information regarding Study Visit Month 9.
- Notify pharmacy of patient assignment.

Breakthrough/Relapser Patients: Randomization Visit (R00)

The R00 visit is the first visit of the Randomization Phase for the Breakthrough/Relapse patients in the Treatment or Control arm of the trial. Those in the treatment group will receive the appropriate dose of Peginterferon alfa-2a 90 μg. Those in the Control Arm will not receive any study medications. Required testing and interviews are:

R00 Breakthrough/Relapse Patient administered questionnaires

- Alcohol use (Form #42)
- Symptoms (Form #43)
- Beck Depression Inventory (Form #44)
- Form #140: Physical Activity
- Form #141: Analgesic Medication

R00 Breakthrough/Relapse Interviews

- Medications Interview (Form #12)

R00 Breakthrough/Relapse Tests

- Endoscopy (Form #23). The endoscopy must be performed within 4 weeks of Randomization Visit (R00) for those patients being randomized. See Section R of the MOO, Endoscopy, for further information.

R00 Breakthrough/Relapse Local lab tests (Form #30)

- Liver chemistries (AST, ALT, alkaline phosphatase, total bilirubin, albumin, and globulin [or total protein])
- Complete blood count with diff (WBC, neutrophils, hematocrit, hemoglobin, platelets
- Pregnancy test (for women of child bearing potential)

- INR
- Uric Acid

R00 Breakthrough/Relapse Central lab tests (Forms #31 and #32)

- HCV-RNA (sent to central repository for shipping for the central virology lab. This specimen will be sent to the repository but not tested and reported until later in the study.

R00 Breakthrough/Relapse Forms

- Form #12: Medications Interview
- Form #15: CTP
- Form #23: Endoscopy
- Form #26: Peginterferon Accountability Log
- Form #28: Peginterferon Dose Adjustment Log
- Form #30: Local Lab
- Form #31: Central Lab—HCV-RNA (tested and reported later in the study)
- Form #42: Alcohol Use
- Form #43: Symptoms
- Form #44: Beck Depression Inventory
- Form #77: Randomization Visit (R00) Aliquot Form
- Form #98: R00 Visit Date
- Form #140: Physical Activity
- Form #141: Analgesic Medication

R00 Breakthrough/Relapse Instructions to Treatment Arm Patients

- Collect all vials of Peginterferon alfa-2a 180 μg and record return on Form #26: Peginterferon Accountability Log.
- Collect all ribavirin and record return on Form #27: Ribavirin Accountability Log.
- Dispense trial medications. Patients will receive Peginterferon alfa-2a 90 μg sc weekly in the Randomized Phase. Record dispensation of drug on Form #26: Peginterferon Accountability Log. (If the patient was taking 45 μg at the time of randomization to treatment, s/he may remain on that dose.)
- Give medication instructions and follow up information regarding Study Visit Month 9.
- Record Peginterferon dose adjustment on Form #28: Peginterferon Dose Adjustment.
- Record ribavirin dose discontinuation on Form #29: Ribavirin Dose Adjustment.
- Notify pharmacy of patient assignment.

R00 Breakthrough/Relapse Instructions to Control Arm Patients

- Collect all vials of Peginterferon alfa-2a 180 μg and record return on Form #26: Peginterferon Accountability Log.
- Collect all ribavirin and record return on Form #27: Ribavirin Accountability Log.
- Give follow up information regarding Study Visit Month 9.
- Record Peginterferon dose adjustment on Form #28: Peginterferon Dose Adjustment.
- Record ribavirin dose discontinuation on Form #29: Ribavirin Dose Adjustment.
- Notify pharmacy of patient assignment.

Randomization Phase Patient Visits

All patients entering the Randomization Phase, whether a Lead-in Group patient, an Express Group patient or a Breakthrough/Relapse patient will follow the same protocol for the HALT-C Trial, with a few exceptions noted below.

Patient visits for remainder of Randomization Phase:

- All patients will be seen every 3 months through Month 48 (M48).
- There will be one additional follow up visit at month 54 (M54).
- For a small number of patients one or two Extended Follow-up Visits at month 60 (M60) and month 72 (M72) (see D.6: Extended Follow-up Visits for detailed information.)

Patients assigned to the Treatment Arm will remain on treatment through Month 48 (M48) or through January 31, 2007, whichever comes first. Patients will receive Peginterferon alfa-2a 90 μg sc weekly. Dispense medications at each visit. Notify the pharmacy that the patient is randomized to receive treatment. Required testing and interviews are:

Randomized Phase Visit patient administered questionnaires

- QOL (Form #40) to be completed annually, and at M54
- Alcohol use (Form #42) at M12, M18, M24, M30, M36, M42, M48
- Symptoms (Form #43) to be completed at every visit
- Beck (Form #44) to be completed at every visit
- Block Food Frequency questionnaire to be completed at M18 only
- Smoking History (Form #142) to be completed at M09 by Express patients only.
- Current Cigarette Smoking (Form #143) to be completed at M24 and M48
- Hormones and Women (Form #144) to be completed at M09 by Express patients only.
- Weight History (Form #146) to be completed at M09 by Express patients only.

Randomized Phase Visit Interviews

- Study Visit (Form #10) to be completed at every visit
- Medications Interview (Form #12) to be completed at every visit
- Life Events Status (From #45) to be completed annually, and at M54

Randomized Phase Visit Tests

- Physical exam (Form #11) to be completed at every visit
- Ultrasound (MRI, CT) evaluation of the liver: to be done annually (see Section R of the MOO for additional information on this procedure) (Form #22)
- Endoscopy evaluation (Form #23) at M24 for selected patients (patients for whom varices were detected at W24) and at M48 for all patients. See Section R of the MOO for additional information on this procedure.
- Liver Biopsy (Forms #14 and #52) to be performed at M24 + M48

Randomized Phase Visit Local lab tests (Forms #30 and #34)

- Fasting serum chemistries at M12, M18, M24, M30, M36, M42, M48
- (BUN, creatinine, glucose, uric acid, triglycerides)
- Liver function tests at every visit (AST, ALT, alkaline phosphatase, total bilirubin, albumin, and globulin [or total protein])
- Complete blood count with diff at every visit (WBC, neutrophils, hematocrit, hemoglobin, platelets)
- Prothrombin time (INR) at every visit
- Alfa-fetoprotein (AFP) at every visit (Form #34)
- Thyroid stimulating hormone (TSH) at M12, M18, M24, M30, M36, M42, M48

- Pregnancy test (for women of child bearing potential) at M09 + M12
- Urinalysis of heme and protein at M12, M24, M36 + M48

Randomized Phase Visit Central lab tests (Forms #31, #73)

- HCV-RNA at M12, M18, M24, M30, M36, M42, M48 + M54 sent to central repository for shipping for the central virology lab.

Randomized Phase Visit Serum aliquots for repository at every visit

- Whole blood for DNA at M9, M15, M21, M27
- Whole blood for PBMC at M21, M45, M54 for the following selected patients:
- Patients who have consented to participate in the Immunology / Virology Ancillary Studies have PBMC specimens collected at the Month 21 (M21) and Month 45 (M45) visits.
- Patients who had M21 PBMC specimens collected before February 1, 2003 will have PBMC specimens collected at the M45 visit.
- All other patients will not have PBMC collected at the M21 or M45 visits.

Randomized Phase Visit Consent for Extended Follow-up Visits

- A consent form for selected patients will be signed at the Month 48 Study Visit. If the patient agrees to Study Month 60 and Study Month 72, the data entering of the consent form (Form #604) will trigger the Month 60 and Month 72 visits to appear in the DMS. See Extended Follow-up Visits Section D6 of the Trial Phases for further details.

Randomized Phase Visit Forms

- Form #10: Study Visit
- Form #11: Physical Exam
- Form #12: Medications Interview
- Form #14: Specimen Collection
- Form #15: CTP Score
- Form #22: Ultrasound, MRI, CT
- Form #23: Endoscopy
- Form #30: Local Lab
- Form #31: Central Lab-HCV RNA
- Form #34: AFP
- Form #40: Quality of Life
- Form #42: Alcohol Use
- Form #43: Symptoms
- Form #44: Beck
- Form #45: Life Events Status
- Form #51: Central Pathology Review (M24 + M48 only)
- Form #52: Clinical Center Biopsy (M24 + M48 only)
- Form #73: Randomized Phase Aliquot Form
- Form #110: Central Endoscopy (completed by Central Endoscopy Committee and data entered at DCC)
- Form #142: Smoking History, Express patients only.
- Form #144: Hormones and Women, Express patients only.
- Form #146: Weight History, Express patients only.
- Form #181: Histopathology (M24 + M48 only)
- Form #183: Serum Iron (M24 + M48 only)
- Form #604: Extended Follow-up Consent, selected patients, only.

Randomized Phase Visit Instructions to Treatment Arm Patients

- Collect and dispense Peginterferon alfa-2a 90 μg vials and record on Form #26: Peginterferon Accountability Log.
- Give medication instructions and follow up information regarding next Study Visit.

Randomized Phase Visit Instructions to Control Arm Patients

- Give follow up information regarding next Study Visit.

Form Completion and Data Entry after a Missed Visit

Once a patient is randomized, strongly encourage him or her to remain in the trial. Unless the patient says, "don't ever contact me again", you need to contact him or her at 3-month intervals to see how he or she is doing and to collect as much study data you are able to collect. To see a list of patients who have missed a visit, go to Reports/Data Management Reports in the DMS and select "List Missed Visits".

- Complete Form #24: Missed Visit every time the patient does not come in for a visit. This is an addable form in the DMS. To add this form go to the visit that was missed and click on "Additional Forms" at the bottom of the "Summary of Forms" screen. Select Form #24 and click OK. That form will now be available for entry.
- Complete Form #924: Alternative Study Visit for every two consecutive missed randomized visits. This is an addable form in the DMS. Add it to the second of the two consecutive missed visits.

If the patient missed a visit in the Randomized Phase of the HALT-C Trial, tests, procedures, or forms might be collected at a later visit. Priorities of data collection are liver biopsy, ultrasound, and endoscopy. Every effort should be made to complete these "catch-up" procedures as soon after the missed visit as possible. Blood collection for the Main Trial and Ancillary Studies and missed questionnaires may also be done at the next in-person study visit if the patient is willing.

Liver Biopsy: If the patient does not come in for the M24 visit, but does come in at M27, you should still do a liver biopsy. Liver biopsy comparison is a main hypothesis in the trial. If the patient does not come in at the exact time, and is difficult to get in, the liver biopsy should be performed as close to its due date as possible. If you know the patient will be in for the M21 visit, but then may withdraw, schedule the liver biopsy early.

- Complete Form #14: Specimen Collection and enter it in the DMS in the M24 visit.
- Complete Form #52: Clinical Center Biopsy and enter it in the DMS in the M24 visit.

Telephone Interviews: Ideally the patient should come into the clinic, but if that is not possible, you can fill out forms by telephone or have the patient send in questionnaires, depending on IRB approval at your site. Please confirm this with your IRB before conducting telephone interviews. Please write a comment on the paper form stating that the interview was conducted by telephone. Enter the same comment as a Form Level Comment in the DMS.

Non-Trial Interferon: If a patient is a control and starts taking interferon prescribed by his or her PCP, the patient remains in the trial. On Form #12: Medications Interview record interferon as a prescribed medication.

Guidelines for form completion and data entry into the HALT-C Data Management System (DMS) when forms have been collected after a missed visit:

- "Visit Date" and "Date Form Completed" are the actual date of the current visit or procedure.
- "Visit number" is the number of the missed visit.
- To enter a form that has been set to missing in the DMS, go to appropriate Study Visit. Click the blue icon next to the corresponding form. Click "Reset to Expected". Data enter the form.
- A validation check may be triggered in the DMS when entering dates. The data manager should enter the comment, "Data (or name of procedure) collected at the M## visit" and set the override.
- Physical exams are required at every visit. However, at M12, M24, M36 and M48, a more complete physical exam is required (Form #11, Section B). In the event that one of these visits is missed, you will need to do a complete physical exam when the patient comes in for the next visit (M15, M27, M39, M54). Complete one Form #11 and data enter it in the missed visit (M12, M24,

M36, M48). Set Form 11 Physical Exam to missing in the current visit (M15, M27, M39, M54) with the reason, "Form 11 entered in M## visit".

- When "catch-up" local lab blood is collected after a missed M12, M24, M36 or M48 visit, complete one Form #30 Local Lab and data enter it in the missed visit. Set Form #30 to missing in the current visit (M15, M27, M39, M54) with the reason, "Form 30 entered in M## visit."
- CTP scores are also required at every visit. However, when the CTP score is collected after a missed visit M12, M24, M36 or M48, you will need to enter the Form #15 CTP Score in the missed visit so that it is in the same visit as the Form #11 Physical Exam and Form #30 Local Lab. Set Form #15 CTP Score to missing in the current (M15, M27, M39, M54) visit with the reason, "Form 15 entered in M## visit."
- When aliquots are collected after a missed visit, fill out **two** Randomized Phase Aliquot Forms (Form #73) and use **two** sets of labels. Fill out one aliquot form and use the set of labels for the current visit. Then fill out another aliquot form and use the set of labels from the missed visit.
- When biopsies are obtained at visits other than M24 or M48, fill out Form #14, Form #52, and the M24/M48 Randomized Phase Aliquot Form (Form #73). Use the set of labels from the M24 or M48 missed visit.
- Ancillary Studies Aliquot Forms may need to be entered only in the current visit, only in the missed visit, or both. Always enter the AS Aliquot Forms in the visit for which the specimen is required.
- Some AS Forms are required at two consecutive visits. If a visit is missed, only collect data and specimens for the later visit.

Example 1: A patient missed his M24 visit but he came in on 09/27/2004 for the M27 visit and has the ultrasound that he missed at M24. The coordinator completes the Form #22 Ultrasound entering "M24" as the Visit Number and "09/27/2004" as the Visit Date. In the DMS, the data manager goes into the M24 visit and clicks on the blue icon for Form #22. The data manager then clicks "Reset to Expected" and data enters the Form #22.

Example 2: A patient missed her M36 visit but agrees to have the missed blood specimens collected when she comes in for her M39 visit on 09/30/2004. Collect the usual M39 blood specimens and use the M39 labels. Record these specimens on the M39 aliquot form (Form #73) and data enter in the M39 visit. Collect the additional M36 specimens and use the M36 aliquot labels. Record these specimens on a M36 aliquot form (Form #73). Data enter in the M36 visit and add the comment "Blood collected at M54 visit". Complete Form #11, Form #15 and Form #30 Local Lab using M36 as the visit number. Use the date of actual M39 visit. Data enter Form #11, Form #15 and Form #30 in the missed M36 visit after resetting the forms to Expected. Set the Form #11, Form #15 and Form #30 under M39 to missing with the reason, "Form ## entered in M## visit."

Example 3: Form #175 is required at both M48 and M54. M48 is missed, but the Coordinator is able to collect NA (seq.301) and Replication (seq. 320) at M54 for the missed M48 visit. QS (seq.302-303) is collected for the M54 visit. Enter Form #175 with the NA and Replication specimens in M48. Enter the Form #175 with the QS in M54.

Example 4: The LP Aliquot Form #273 and Cognitive Effects Forms (Form #150, #152, #153, #154, #156) are collected at both M48 and M54. M48 is missed, so the forms are only be filled out once and entered in M54.

Permanent Discontinuation of Trial Medications

If the patient is permanently discontinued from trial medication, s/he should still be followed through Study Visits Month 54, 60 and 72, as applicable. The following conditions will lead to the permanent discontinuation of trial medications:

- Pregnancy
- Liver transplant
- Hepatocellular carcinoma (HCC)
- UNOS Status 2b, as defined by the 1999 UNOS Transplant Criteria Meeting
- Intolerant or non-compliant of trial medication
- Patient withdraws consent/refuses follow up
- Patient is not compliant of visits.
- Patient is lost to follow up.

Document as follows:

- Document in the medical record that the patient is being permanently discontinued from trial medication and the reason.
- Notify the pharmacy.
- Complete Form #19: Early Termination of Peginterferon Treatment.
- Collect Peginterferon alfa-2a 90 μg vials and record on Form #26: Peginterferon Accountability Log.
- Record Peginterferon dose adjustment on Form #28: Peginterferon Dose Adjustment.

Permanent Discontinuation of Trial Participation

Because we will use an "intent to treat" analysis, every attempt should be made to continue to follow patients once they have been randomized. Once a patient is randomized, s/he will be included in all trial analyses. If a randomized patient withdraws consent or refuses further follow up, the consequence is early permanent termination of trial participation.

Document as follows:

- Document in the medical record that the patient's participation in the trial is being permanently discontinued and the reason.
- Complete Form #25: Early Termination from Trial. This form is an addible form. Add it to the patient's last completed visit. For example, if the patient finished M12 and is leaving before M15, enter the Form #25 into the M12 visit.

Complete all applicable outstanding forms or pending edits for this patient:

- Run the "Site Outstanding QC report" by going to Reports/Tracking. Send all outstanding QC to NERI for double-data-entry.
- Run the "Upcoming Visit Data Cleaning" by ID by going to Reports/Patient Visit Related. This report lists pending edits, expected forms, expected Block Food Questionnaires, peginterferon/ribavirin dose/dispense and dose adjustment reports, and outstanding AEs and SAEs. Complete data entry for every form that is still outstanding, resolve edits, and send Blocks to NERI. Check all medication logs and close out all AEs and SAEs as outlined below.
- Check all the medication logs to make sure they are complete and up-to-date.
    - If the patient was in the Treatment Arm:
        - Complete Form #19: Early Termination of Peginterferon Treatment if the patient is leaving before M48 visit. This is an addible form in the DMS. Add it to the visit that the patient stopped the peg. If the patient stopped the Peginterferon between two visits, add it to the later visit. For example, if the patient stopped the peg between M12 and M15, enter the Form #19 into the M15 visit.
        - Collect all vials of Peginterferon alfa-2a 180 μg and record return on Form #26: Peginterferon Accountability Log. The number of vials given out to the patient should equal the number dispensed. If not, complete a Form #926: Lost Drug Accountability Log for lost drugs.
        - Record Peginterferon dose adjustment to "0" on Form #28: Peginterferon Dose Adjustment.
        - After the patient was randomized, there should be a documented dose adjustment to "0" on Form #29: Ribavirin Dose Adjustment.
    - If the patient was in the Control Arm:
        - After the patient was randomized, there should be a documented dose adjustment to "0" on Form #28: Peginterferon Dose Adjustment and Form #29: Ribavirin Dose Adjustment.
- Make sure all adverse events are resolved and so documented. Remember that if the Adverse Event became a Serious Adverse Event and the SAE is resolved, the Adverse Event should also be resolved.
- Run tracking reports (Expected Biopsy, Endoscopy, CIDI and Site Freezer Inventory) by going to Reports/Tracking in the DMS. Make sure everything is sent to NERI or the appropriate lab or the Repository if applicable. Double-check the freezer for specimens that need to be sent for this patient.

Patient Death

Because we will use an "intent to treat" analysis, randomized patients who have died will be included in all trial analyses.

Document as follows:

- Document in the medical record that the patient's has died.
- Complete Form #60: Adverse Event related to the death.
- Complete Form #61: Serious Adverse Event related to the death.
- Complete Form #63: Clinical Outcome for the death.
- Complete Form #64: Death Report. This is an addible form in the DMS. Add it to the "Adverse Event" Category.
- Follow QxQs and Protocol for further information regarding completion of these forms.

Complete all applicable outstanding forms or pending edits for this patient.

- Run the "Site Outstanding QC report" by going to Reports/Tracking. Send all outstanding QC to NERI for double-data-entry.

- Run the "Upcoming Visit Data Cleaning" by ID by going to Reports/Patient Visit Related. This report lists pending edits, expected forms, expected Block Food Questionnaires, peginterferon/ribavirin dose/dispense and dose adjustment reports, and outstanding AEs and SAEs. Complete data entry for every form that is still outstanding, resolve edits, and send any Block Food Frequency Questionnaires to NERI.

- Check all the medication logs to make sure they are complete and up-to-date.
  - *If the patient was in the Treatment Arm:*
    - Complete Form #19: Early Termination of Peginterferon Treatment if the patient is leaving before M48 visit. This is an addible form in the DMS. Add it to the visit that the patient stopped the peg. If the patient stopped the Peginterferon between two visits, add it to the later visit. For example, if the patient stopped the peg between M12 and M15, enter the Form #19 into the M15 visit.
    - Collect all vials of Peginterferon alfa-2a 180 μg and record return on Form #26: Peginterferon Accountability Log. The number of vials given out to the patient should equal the number dispensed. If not, complete a Form #926: Lost Drug Accountability Log for lost drugs.
    - Record Peginterferon dose adjustment to "0" on Form #28: Peginterferon Dose Adjustment.
    - After the patient was randomized, there should be a documented dose adjustment to "0" on Form #29: Ribavirin Dose Adjustment.
  - *If the patient was in the Control Arm:*
    - After the patient was randomized, there should be a documented dose adjustment to "0" on Form #28: Peginterferon Dose Adjustment and Form #29: Ribavirin Dose Adjustment.

- Make sure all adverse events are resolved and so documented. Remember that if the Adverse Event became a Serious Adverse Event and the SAE is resolved, the Adverse Event should also be resolved.

- Run tracking reports (Expected Biopsy, Endoscopy, CIDI and Site Freezer Inventory) by going to Reports/Tracking in the DMS. Make sure everything is sent to NERI or the appropriate lab or the Repository if applicable. Double-check the freezer for specimens that need to be sent for this patient.

Transfer of patient from Site #1 to Site #2

Site #1 (original Site of patient) will:

1. Have the patient sign release of records and information before talking or sending any records to Site #2 (Site to which the patient wishes to transfer).

2. Make sure everything is data entered. Run the "Upcoming Visit Data Cleaning by ID report", which lists pending edits and expected forms. Run the "Site Outstanding QC report". Complete and data enter everything that Site #1 is responsible for.

3. Make sure all adverse events are resolved and so documented. Remember that if the adverse event became a Serious Adverse Event and the SAE is resolved, the adverse event should also be resolved. The "Upcoming Visit Data Cleaning by ID report" has a list of outstanding AE and SAEs.

4. Check all the medication logs to make sure they are complete and up-to-date.

5. If the patient is involved in any Ancillary Study at Site #1, and Site #2 is not in the same Ancillary Study, complete a withdrawal form and enter it into the DMS. If Site #2 is involved in the same Ancillary Study, then the patient can continue in the study. Ancillary Studies Withdrawal Forms are: Form #155: Cognitive Effects, Form #176: Immunology/Virology and Form #194: QLFT.

6. Copy the following paper forms and send to Site #2:
   - All adverse events (Form #60) and serious adverse events (Form #61).
   - All ultrasound, MRI, or relevant CT scan reports for comparison with future reports.
   - All liver biopsy reports.
   - Any clinical outcome forms (Form #63) and documentation.
   - Lab flow sheet.
   - Nurse's notes from the last visit with a summary.
   - PI summary of medical history and update.
   - Drug Accountability Logs (Forms #26, #27) and Dose Adjustment Logs (Forms #28, #29).
   - Any other relevant material.

7. Send all the labels to Site #2; the ID labels and the aliquot labels.

8. Be sure to check the freezer for specimens that need to be sent for this patient. Run tracking reports (Expected Biopsy, Endoscopy, Block Tracking, CIDI and Site Freezer Inventory).

9. Let Site #2 know which forms or specimens are still outstanding. Are all the Block Food Questionnaires returned? Did the patient bring back the breath specimens for QLFT?, etc.

10. Send new contact information of patient with telephone #.

NERI will:

Once Site #1 has contacted Site #2, data entered all outstanding forms and pending edits and sent the relevant material, let NERI know and the patient's record in the DMS will be transferred to the new Site. When the transfer is complete, Site #1 will not be able to access that patient in the DMS, and Site #2 will have the patient accessible to them.

Site #2 (Site to which the patient wishes to transfer) will:

Make an appointment and have the patient sign a new consent form for Site #2. The patient is usually the one to contact the new Site to set up an appointment.