HALT-C Trial Phases

Introduction

The Hepatitis Antiviral Long-term Treatment against Cirrhosis Trial (HALT-C) is a multi-center, randomized, controlled trial to evaluate the safety and efficacy of long term Peginterferon alfa-2a use in patients with chronic hepatitis C and bridging fibrosis or cirrhosis, who have failed to respond to previous interferon therapy. The purpose of the study is to determine if long-term therapy can reasonably reduce the risk of progression to more advanced liver disease. The HALT-C Trial has distinct phases: Screening, Lead-in, Responder, Randomized, and Extended Follow-up Phases.

Screening Phase

During the Screening Phase, patients are evaluated for eligibility to enroll in the HALT-C trial. Two groups of patients may enter the Screening Phase.

- Lead-in Group patients have been non-responders to their most recent course of interferon treatment prior to entry into the Screening Phase.
- Express Group patients have had a parallel treatment of interferon/ribavirin combination prior to entry into the Screening Phase.

Lead-in Phase

Lead-In Group patients will be offered 24 weeks of combination Peginterferon alfa-2a/ribavirin treatment during the Lead-in Phase.

Responder Phase

Patients who respond to the Lead-in treatment (no detectable HCV-RNA at the Week 20 visit) will be followed for up to 48 additional weeks in the Responder Phase, for a total of 72 weeks of follow-up. Responder Phase patients are treated with combination Peginterferon alfa-2a/ribavirin for an additional 24 weeks (Weeks 24 to 48). 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. Sustained Virologic Responder patients have no detectable HCV-RNA throughout the Responder Phase, and complete their participation in the Trial at the Week 72 visit.

Randomized Phase

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. There are three different ways to enter the Randomization phase:

- Express Group patients can be enrolled directly into the Randomization Phase after eligibility is confirmed during the Screening Phase.
- Lead-in Group patients who do not respond to the Lead-in treatment (detectable HCV-RNA at the Week 20 visit during the Lead-In Phase) are 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.

In January 2007, all Peginterferon alfa-2a treatment in the Randomized Phase Treatment Arm will end. A small number of patients may not have completed 3.5 years of low-dose Peginterferon alfa-2a treatment at that time. Nonetheless, every patient will stop treatment at that time point.

Extended Follow-up Phase
Patients who entered the Trial early and therefore complete the Randomized Phase early will be offered "extended follow-up" visit(s) through April 2007. These visits will primarily be to identify outcome events, and to provide information to patients concerning the current status of the trial.

Data Form Completion and Source Documentation
All data forms for the HALT-C Trial should be completed using black ink. Cross outs should consist of a straight line through the error with the data recorder's initials and date of change. Writing in the margins is discouraged, but, if necessary, indicate clearly by circling the writing and add "not for data entry". Otherwise, information written on the form will be data entered. Detailed instructions called QxQs are available for most forms. See the Data Management, Visit Schedule, and Forms and QxQs sections of the Manual of Operations for more details.

Visit numbers
Study weeks and months are identified by a letter (S, R, W, or M) and a two-digit number.

Screening Phase:	S00
Lead-in Phase:	W00 (Baseline) through W24 (week 24)
Responder Phase:	W30 (week 30) through W72 (week 72)
Randomized Phase:	M09 (month 9) through M54 (month 54)
Extended Follow-up Phase:	M60 (month 60) and M72 (month 72)

Express, Breakthrough, and Relapse patients also have a R00 visit. For Express patients, the R00 visit is also their Baseline visit. For Breakthrough and Relapse patients, the R00 visit marks their entry into the Randomized Phase.

Source documents
A source document is a part of the patient's medical record which serves to validate the data collected on data entry forms. The following source documentation will be accepted:

- Medical history, previous interferon treatment, non-response to treatment, adequate contraception, medications: Notations in a clinic note, hospital or other medical records. The clinic note may document a phone call with a previous provider.
- Ultrasound (MRI, CT): Ultrasound MRI or CT report, depending on test done.
- Liver biopsy: Pathology report
- Endoscopy: Endoscopy report and photos
- Lab results from blood tests: Lab report
- Lab results from urine dipstick and pregnancy test: Clinic note
- CIDI: Printed diagnoses list from computer and CIDI electronic file
- Case report forms requiring signature if not documented in clinical note: (Forms #3, 6, 7, 10, 11, 12, 45, 61).

Source document by form
a. Form #1: Trial ID Assignment
   - Notation in the medical record of prior treatment with interferon
   - Lab report (or, if not available, a clinic note) for (+) HCV-RNA OR Lab report for serum ALT elevation despite treatment with interferon
b. Form #3: Screening Medical History
   - Interviewer's signature denotes that all items on the form have been reviewed with the patient and/or by chart review.
c. Form #4: Screening Checklist
   - Lab report for (+) HCV antibody
   - Lab reports for iron, TIBC, ferritin, ANA, Hep B surface antigen, HIV serology

- Printed diagnoses list for CIDI
- Notation in medical record from consulting psychiatrist/psychologist that the patient is eligible for trial if patient had a previous psychiatric illness while on interferon.

d. Form #6: Baseline History
   - Notation in the medical record or signature of interviewer and PI physician.
e. Form #7: Screening Medications Interview
   - Notation in the medical record or signature of interviewer
f. Form #10: Study Visit
   - Notation in the medical record or signature of interviewer
g. Form #11: Physical Exam
   - Notation in the medical record or signature of person performing the examination
h. Form #12: Medications Interview
   - Notation in the medical record or signature of interviewer
i. Form #19: Early Termination of Peginterferon Treatment
   - Notation in the medical record
j. Form #22: Ultrasound (MRI, CT)
   - Ultrasound, MRI or CT report, depending on test done.
k. Form #23: Endoscopy
   - Endoscopy report
   - Endoscopy photos
l. Form #24: Missed Visit
   - Notation in the medical record
m. Form #28: Peginterferon Dose Adjustment Log
   - Notation in the medical record
n. Form #29: Ribavirin Dose Adjustment Log
   - Notation in the medical record
o. Form #30: Local Lab
   - Lab report for CBC with differential, LFTs, chemistries, uric acid, PT
   - Notation in the medical record for urine dipstick and pregnancy test

Proper procedure for identifying source documentation

The source documents should be available. For any source documentation sent outside of the clinical site, identifying information, such as patient name and medical record should be blacked out and replaced with the patient ID number (labels provided by the DCC can be used.)

Storage of forms and source documents

Forms should be stored in their binders. Source documents should be available. Binders should be stored in a room or other storage space that can be locked. Access should be limited to appropriate personnel.