(Study Discontinued on 07/19/2002)

Effects of Interferon on Portal Hypertension Ancillary Study

Principal Investigator: Arun J. Sanyal

I. Specific Aims

The HALT-C Trial will evaluate the ability of long-term interferon (IFN) treatment to inhibit the progression of chronic hepatitis C virus (HCV)-related liver disease in non-responders to interferon/ribavirin therapy.

The specific hypothesis to be tested in the portal hypertension ancillary study is:
Long-term interferon therapy in patients with hepatitis C-related cirrhosis inhibits the development and progression of portal hypertension and the development of gastro-esophageal varices.

This hypothesis will be tested by the following specific aims:

1. To perform a prospective, randomized controlled trial to compare the efficacy of long-term interferon therapy to no treatment for the prevention of development of gastro-esophageal varices in cirrhotic patients without varices who enter the HALT-C Trial.

   All patients with cirrhosis and no varices at the time of randomization will be studied. Varices will be assessed by endoscopy at randomization and year 04 (M48). Development of portal gastropathy is a secondary endpoint.

2. To perform a prospective, randomized controlled study of the effects of long-term interferon therapy to no treatment on the hepatic venous pressure gradient (HVPG) and hepatic hemodynamics in cirrhotic patients with either small or no varices who enter the HALT-C Trial.

II. Studies Related To Specific Aim # 1:

Participating centers:
All HALT-C clinical centers.

Objective:
To determine if maintenance IFN therapy lowers the rate of development of varices in IFN/ ribavirin non-responders with HCV-related cirrhosis and no varices compared to untreated controls.

Rationale and Justification:
If long-term IFN therapy decreases progression of hepatic fibrosis, the central hypothesis of the HALT-C Trial, it should decrease portal hypertension, development of varices, variceal enlargement and hemorrhage. This ancillary study focuses on development of varices as the primary endpoint.

Entry criteria and method of enrollment:
Patients with cirrhosis (an Ishak fibrosis score of 5 or 6 upon central biopsy review) but no varices on endoscopy performed within 4 weeks of randomization .

All patients will have a liver biopsy prior to being enrolled in the HALT-C Trial. Those with biopsy-proven cirrhosis as evaluated by the Central Pathology Committee (Form 51) will have a baseline endoscopy performed within 4 weeks of randomization. Those who have cirrhosis (an Ishak fibrosis score of 5 or 6) but no varices will be entered in this study.

Initial endoscopy:
The objective of this initial baseline endoscopy (at randomization) will be to document the presence or absence of esophageal varices, gastric varices and portal gastropathy. This will provide valuable baseline data, which will be used, for comparison with findings from subsequent endoscopies.

Endoscopy Procedures:
Panendoscopy will be performed using conscious sedation in most cases. Appropriate safety guidelines, as defined by the American Society of Gastrointestinal Endoscopy will be used during the procedure.

A. Esophageal varices:
These will be assessed in the distal 5 cm of the esophagus with air-insufflation of the esophagus. The following parameters will be noted:

- # of columns of varices
- Extent of varices
- Size of varices: small, medium and large corresponding to F1-F3 of the NIEC classification.
  F1: small, straight varices
  F2: enlarged, tortuous but occupying less than a third of the lumen
  F3: enlarged, tortuous and occupying more than a third of the lumen
- Red signs:
  a. red wale marks: red streaks along the long axis of the varices
  b. hematocystic spot: a blood blister on a varix
  c. varix on varix: a superficial vein overlying a varix

B. Gastric varices:
These will be identified and classified according to Sarins classification as:

- Gastro-esophageal varices (GOV) type 1: gastric varices in continuity with esophageal varices along the lesser curve of the stomach.
- Gastro-esophageal varices (GOV) type II: gastric varices in continuity with esophageal varices along the greater curve of the stomach.
- Isolated gastric varices (IGV) type I: isolated cluster of varices in the fundus of the stomach.
- Isolated gastric varices (IGV) type II: isolated varices in regions of the stomach other than in the fundus.

Endoscopic assessment and scoring of portal gastropathy:
The following definitions will be used for purposes of this study by the investigators:

1. Mosaic pattern (MP): small polygonal areas demarcated by a distinct white-to-yellow border and with a slight central bulge, which have a mosaic, fish scale-like appearance upon endoscopy. The mosaic pattern will be considered to be mild when the color of the mucosa is pink while diffuse erythema (redness) of the mucosa will be considered to represent severe MP.
2. Red Marks: flat or slightly bulging red lesions seen in the gastric mucosa. Such lesions include fine punctate hemorrhagic spots and discrete red spots corresponding to the red point lesions and cherry red spots described by the NIEC group (1). When present in isolated discrete spots, they will be given a score of 1 while confluent areas of submucosal hemorrhage will be given a score of 2 (table 1).
3. Black-brown spots: represent old submucosal hemorrhage and will not be scored. These definitions are identical to those proposed by the NIEC (1) and by Sarin (2) to develop the scoring system for portal gastropathy presented at the Baveno conference.
4. Gastric antral vascular ectasia (GAVE): will be diagnosed by the presence of flat or slightly raised red stripe-like lesions radiating from the pylorus to the antrum and body of the stomach for a variable distance (3).

Calculation of the portal gastropathy score:
The severity of the portal gastropathy will be scored as proposed by Sarin (Table 1) (2). A mild mosaic pattern will be given a score of 1 while severe MP will be scored as 2. Isolated RM will be scored as 1 while confluent RM will be scored as 2. Absence of GAVE will be scored as 0 while the presence of GAVE will be scored as 2. The portal gastropathy will be considered to be mild when the total score is less than or equal to 3 and severe if the score is 4 or greater. Scoring will be performed centrally.

Photodocumentation of endoscopy:
Photographs will be obtained at the following sites: (1) esophagus 5 cm above GE junction, (2) at the GE junction, (3) retroflex view of the GE junction and fundus, (4) corpus and (5) antrum of stomach. Photographs will be labeled with patient ID and visit # (entry or exit). Two sets of photographs will be obtained in each case. One set will remain on site in the patient's record. The second will be sent to the DCC for blinded review. Photographs will be reviewed in a blinded manner at the DCC by the investigators for comparison with data recorded on site.

Analysis plan:
1. The rates of de novo development of varices in the two study arms will be analyzed using a chi-square or Fishers exact test depending on the event rate and the relative risks and 95% confidence intervals obtained. The number of subjects with varying grades of varices or types of red signs will be similarly analyzed or will simply be enumerated depending on the event rate.

2. The distribution of portal gastropathy scores at 4 years will be compared using a chi-square test for ordinal data. A method for assigning scores to the data will be developed using the baseline data. The effects of the baseline score or other covariates will be assessed by polytomous logistic regression.

III. Studies Related To Specific Aim # 2:

Participating centers:
- Virginia Commonwealth University
- University of Massachusetts
- University of Michigan

Hypothesis:
Long-term therapy with interferon inhibits the development and progression of portal hypertension in well-compensated cirrhotic subjects with HCV who have failed to clear their HCV viremia with standard interferon/ribavirin therapy.

Objectives:
1. To define the range of HVPG seen in compensated HCV-cirrhosis with either small or no varices and to define the progression of HVPG over time in untreated patients.
2. To prospectively compare the effects of long-term IFN therapy to no treatment on HVPG in cirrhotic subjects with HCV who enter the HALT-C trial.
3. To characterize the superior mesenteric arterial, hepatic arterial and portal venous hemodynamics (splanchnic hemodynamics) in patients with compensated HCV-cirrhosis with small varices and define changes in these parameters over time.
4. To obtain pilot data on the effects of long-term interferon therapy on the splanchnic hemodynamics in patients with compensated HCV-cirrhosis with small varices.

Entry criteria:
Patients with HCV-related cirrhosis (an Ishak fibrosis score of 5 or 6 upon central biopsy review) with small or no varices detected at the randomization endoscopy who are randomized to long-term interferon or no treatment in the HALT-C Trial at the three participating centers.

Interventions (treatment arms):
Long-term interferon (test) vs. no treatment (control)

Methods and parameters to be measured:
1. Hepatic venous pressure gradient measurements will be obtained using the method described by Groszmann et al (see below).
2. Portal vein, hepatic arterial flow and the resistive indices of the superior mesenteric artery and hepatic artery will be measured by transabdominal Doppler ultrasound exams.

The HVPG and ultrasound parameters will be measured prior to randomization in all patients who participate in this part of the portal hypertension ancillary study. For those with no varices by endoscopy at randomization, these parameters will be measured again at the time of exit (M48) from the study. For those with small varices at entry, endoscopy will be repeated after 2 years. If the varices remain unchanged or decrease in size, endoscopy, HVPG measurements and ultrasound exam will be repeated at year 4 (M48). For those with medium to large varices at endoscopy after 2 yrs (M24), the HVPG and ultrasound measurements will be made at this time and the patient will exit the ancillary study. They will also be started on nadolol at this time. Patients for whom medium or large varices are detected at randomization are not eligible for this part of the study. See Appendix 3 of this section (page 13).

Endpoints and plan of analysis:
HVPG is measured on an interval scale. If normally distributed, data from the two treatment arms at entry will be measured by a T-test. Otherwise, a distribution-free tests e.g. a Wilcoxon test will be used. A chi-square test will be used to compare the percent of test and control subjects who show an increase in HVPG to values over 12 mm Hg or a 25% increment over baseline values. These values correlate with the risk of hemorrhage. Mean changes in HVPG will be compared using an analysis of covariance, adjusting for baseline levels. The number of subjects with small varices at entry who develop large varices by yr. 02 or yr. 04 in each arm will be compared using either the Fishers exact test or chi-square test. Regression analysis will be used to examine the interrelationship of changes in hemodynamic parameters and development of varices in this group of subjects.

Measurement of Hepatic Venous Pressure Gradient (HVPG):
All hepatic venous pressure gradient measurements will be made under fasting conditions. Following an overnight fast (NPO after midnight except meds), the procedure will be performed in the angiography suite. These procedures are detailed in Appendix 1 of this section (page 8).

Ultrasound Evaluation of Hepatic Veins, Hepatic Artery And Portal Vein with Color Flow, Doppler and Resistivity Index:
The ultrasound evaluation will be done under fasting conditions. All scans will be performed with ATL HDI 5000 using a 2.5-5.0 MHz probe. The study should include a systematic survey of the liver and spleen. The grey scale, color flow, Doppler and spectral analysis will be performed in transverse, and longitudinal and subcostal views depending on the vessel of interrogation. The color velocity control will be set at 10-20cm/sec for venous and 20-30cm/sec for arterial flow. See Appendix 2 (page 11) for additional information.

It is recognized that superior mesenteric arterial and hepatic arterial flow may not be possible to measure accurately in all individuals. For purposes of data analysis, only those where accurate baseline and post-intervention data can be obtained will be used. Hard copies will be kept on site.

IV. Management Of Portal Hypertension In HALT-C Trial:
The management of patients after the initial endoscopy will depend on the findings. Those without varices will be followed without additional interventions. All those with medium or large esophageal varices as well as gastric varices will be treated for primary prophylaxis of variceal hemorrhage as follows:

Agent to be used: nadolol

Dosage:
Treatment will be initiated with 20-40 mg/day orally (once a day) and the dose titrated upwards until the resting heart rate is between 55-65 beats/min or adverse effects occur preventing further increase or continuation of therapy.

Subsequent endoscopy:
Will be performed at year 04 (M48) for those who have no varices at initial endoscopy. In those with small varices, endoscopy will be performed again at years 02 (M24) and 04 (M48).

What to do for those with large varices who are intolerant of beta blockers:
It is anticipated that up to 15-20% of subjects who are started on beta blockers will have adverse effects requiring discontinuation of the drug. In such cases, further treatment will be provided at the investigator's discretion and after discussion with the patient. Such an option will be necessary because of ethical concerns about withholding potentially life-saving therapy in such subjects.

Management of variceal hemorrhage:
Active variceal hemorrhage will be managed in accordance with accepted clinical guidelines as described by the American College of Gastroenterology (4). The treatment provided will be in accordance with established standard-of-care at individual institutions and individualized to each patient’s clinical circumstances as determined by the treating physician.

BIBLIOGRAPHY

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2. Sarin, S. K. 1996. Diagnostic issues: portal hypertensive gastropathy and gastric varices. In Portal hypertension II. Proceedings of the second Baveno International consensus workshop on definitions, methodology and therapeutic strategies. R. DeFranchis, editor. Blackwell Science, Oxford. 30-55.
3. Gostout, C. J., T. R. Viggiano, D. A. Ahlquist, K. K. Wang, M. V. Larson, and R. Balm. 1992. The clinical and endoscopic spectrum of the watermelon stomach. *J Clin Gastroenterol* 15:256-263.
4. Grace, N. D. 1997. Diagnosis and treatment of gastrointestinal bleeding secondary to portal hypertension. American College of Gastroenterology Practice Parameters Committee. *Am. J. Gastroenterol.* 92:1081-1091.

TABLE 1

Portal hypertensive gastropathy scoring system as proposed at the Baveno consensus conference[2]

Parameter	Score
1. Mucosal mosaic pattern:	
Mild:	1
Severe:	2
2. Red marking:	
Isolated:	1
Confluent:	2
3. Gastric antral vascular ectasia:	
Absent:	0
Present:	2

Mild gastropathy	Score = 3
Severe gastropathy	Score = 4

APPENDIX 1
Hepatic Venous Pressure Gradient (Hvpg)

Introduction
All patients enrolled in the ancillary study "Effects of Interferon on Portal Hypertension" will have Hepatic Venous Pressure Gradient (HVPG) measured with a balloon catheter at prescribed intervals.

Objectives of HVPG
To measure and document hepatic portal venous pressure.

Patient Preparation
- Patient should be fasting (NPO after midnight except for meds)
- Patient should be given the HVPG Patient Information Sheet (located in Appendix F)

Patient exclusion
Patients who have been on any medications that interfere with portal pressure are to be excluded from this measurement. This will include patients on non-selective Beta blockers.

Procedure
1) Sedation: The patient should be sedated using one of the following two types of conscious sedation:
   a) Versed
   b) Fentanyl

2) Premedication: Patients should be premedicated for dye allergies with steroids or benadryl as needed.

3) Pre-op antibiotics will not be used routinely.

4) Apply local anesthetic.

5) Make a right internal jugular or R femoral vein puncture using the Seldinger Technique. Introduce a Cordis sheath into the punctured vein. A 6 French Berestein balloon tipped catheter (available from Medi Tech, Cooper Scientific Corporation, Watertown, MA) will be introduced into the vein.

6) Advance the tip of the catheter about 4-5 cm into the hepatic vein before pressure measurements are made.

7) Calibrate the transducer and recording equipment prior to each tracing using a mercury manometer. A column of water 13 cm high should read 10 mm Hg.

8) For pressure measurement, set the zero reference point 5 cm below the sternum to correspond to the center of the R atrium.

9) The patient should not cough or strain during the pressure measurement, and a stable tracing should be obtained.

10) Pressure tracings are obtained using a Hewlett-Packard recorder at 5 mm/sec speed.

11) Three sets of the following measurements will be taken:
   a) Pressure measurement in the inferior vena cava (IVC) will also be made at the level of the hepatic orifice.

b) Free Hepatic Venous Pressure (FHVP) are then made with the catheter tip free in the hepatic vein (the FHVP should not differ from the IVC pressure by more than 1-2 mm Hg). If the difference between FHVP and the IVC pressure is more than 2 mm, then the free pressure will need to be taken close to the junction of the hepatic vein and the IVC.

c) Inflated balloon measurement
   i) The balloon is then expanded with 2 ml of saline, while the pressure is continuously monitored.
   ii) The wedged position is then confirmed by injecting 1-2 ml of contrast agent into the catheter to demonstrate retention of the dye in the occluded segment of the hepatic vein.
   iii) The balloon is deflated and the dye should flush out.
   iv) The catheter is flushed with normal saline.
   v) The balloon is reinflated.
   vi) Three Wedged Hepatic Venous Pressure (WHVP) measurements are taken. For each measurement, the tracing must be 45-60 seconds long.
   vii) The balloon is then deflated while checking the HVPG and WHVP as often as desired.

Equipment:
- Cordis sheath
- 6 French Berestein balloon tipped catheter (Meditech, Cooper Scientific, Watertown, MA)
- Hewlett-Packard recorder (use at 5 mm/sec speed)
- Tranducer
- Mercury manometer

Weeks of Assessment:
1) Randomization
2) Year 2 (M24) if small varices are present at the randomization endoscopy and medium or large varices are detected on the month 24 endoscopy.
   a) HVPG and Doppler ultrasound measurements will be taken for these patients and then they will exit the study.
3) Year 4 (M48) (all patients remaining on study)
   a) This includes those patients for whom no varices were detected at randomization and either small or no varices were detected at the month 24 endoscopy.

Data Collection:
Form # 111 HVPG Measurement should be completed and data entered at each participating center.

Appropriate Source Documentation:
The following documents must be obtained for each HVPG measurement and attached to Form #111.
- A written report
- Tracings should include the following
  - Zero point
  - Documentation of calibration
  - Recording

Proper procedure for identifying source documents:
The written HVPG measurement report and tracings should be kept with the data entry form. Identifying information such as patient name and medical record number should be blacked out and replaced with the patient ID number (labels provided by the DCC may be used).

APPENDIX 2
Doppler Ultrasound

Introduction:
All patients enrolled in the ancillary study "Effects of Interferon on Portal Hypertension" will have a Doppler Ultrasound performed at prescribed intervals.

Objectives of Doppler Ultrasound:
To perform a systematic survey of the liver and spleen.

Patient Preparation:
- Patient should be fasting (NPO after midnight except for meds)
- Patient should be given the Doppler Ultrasound Patient Information Sheet.

Procedure:
1) A grey scale, color flow, Doppler, and spectral analysis will be in standard fashion. The color velocity control will be set at 10-20cm/sec for venous and 20-30cm/sec for arterial flow.
2) The following views should be observed:
   a) Longitudinal
   b) Transverse
   c) Subcostal

Equipment:
- ATL HDI 5000
- 2.5-5.0 MHz probe

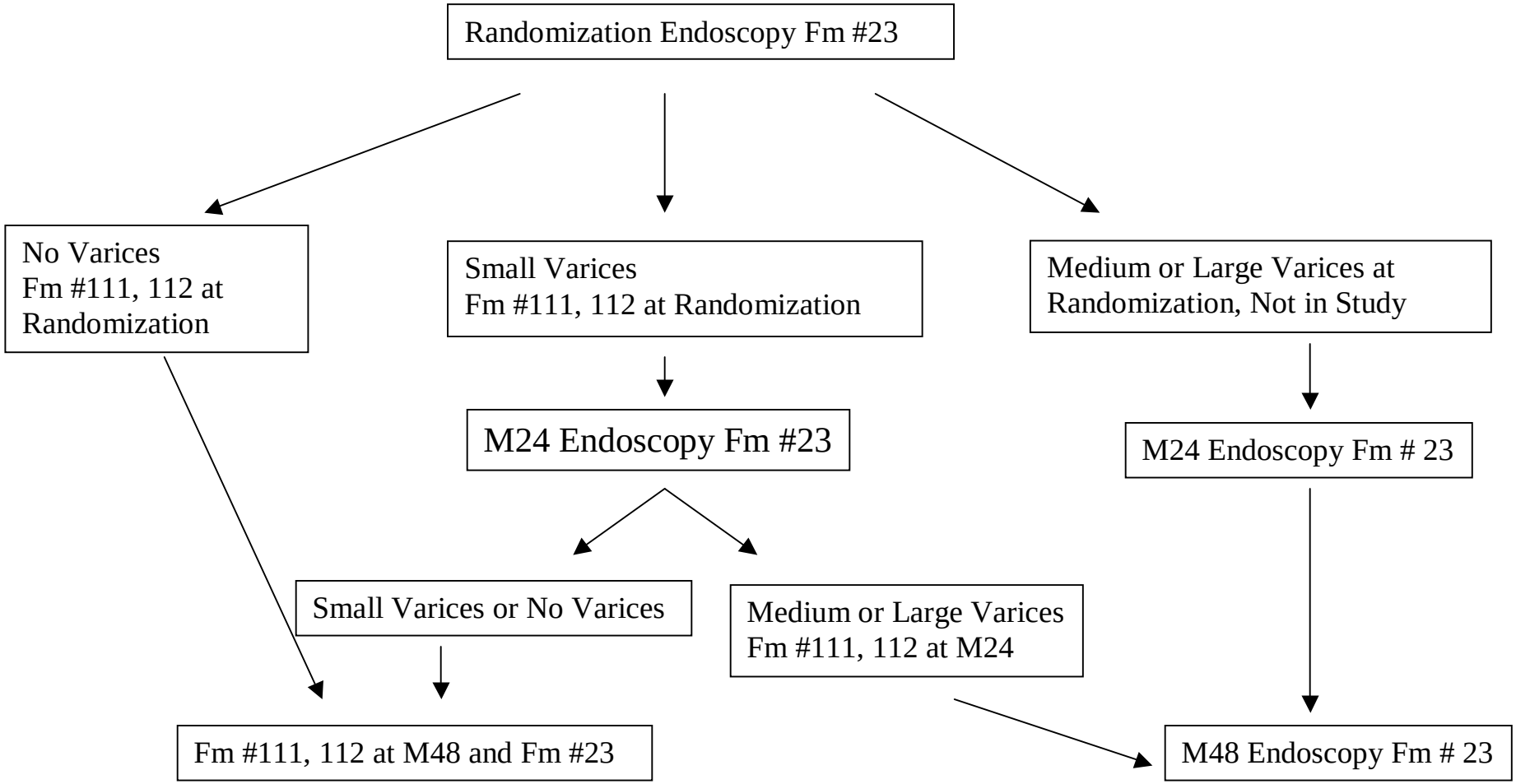
Weeks of Assessment:
1) Randomization
2) Year 2 (M24) if small varices are present at the randomization endoscopy and medium or large varices are detected on the month 24 endoscopy.
   a) HVPG and Doppler ultrasound measurements will be taken for these patients and then they will exit the study.
3) Year 4 (M48) (all patients remaining on study)
   a) This includes those patients for whom no varices were detected at randomization and either small or no varices were detected at the month 24 endoscopy.

Data Collection:
Form # 112 Doppler Ultrasound should be completed and data entered at participating centers.

Appropriate source documentation:
The following documents must be obtained and attached to Form #112 for each Doppler ultrasound:
- A written report
- Pictures of the following views:
  - longitudinal
  - transverse
  - subcostal
- A wave tracing

Proper procedure for identifying source documents:
The written doppler ultrasound report, pictures, and wave tracing should be kept with the data entry form (Form #112). Identifying information, such as patient name and medical record number should be blacked out and replaced with the patient ID number. Labels provided by the DCC may be used.

APPENDIX 3
Portal Hypertension AS Overview



Hepatitis C Antiviral Long-term Treatment against Cirrhosis

HALT-C Trial
Data Coordinating Center

To: **Portal Hypertension AS Sites (UMass/UConn, MGH, UMich, VCUHS)**
From: **Data Coordinating Center**
Re: **Termination of Portal Hypertension Ancillary Study**
Date: **July 16, 2002**

On November 29, 2001, the HALT-C Steering Committee voted to discontinue the Portal Hypertension Ancillary Study due to the limited number of patients who consented to participate. This document records that the Principal Investigator has discussed the Portal Hypertension Ancillary Study's termination with a patient who previously consented to participate in this Ancillary Study. The patient acknowledges data collected prior to the study termination will remain confidential and may appear in scientific publications without identifying the patient by name.

Patient name (please print)_____

Patient signature_____

Date_____

Investigator's name (please print) _____

Investigator's signature_____

Date_____

Hepatitis C Antiviral Long-term Treatment against Cirrhosis

HALT-C Trial
Data Coordinating Center

To: All Study Coordinators
From: Michael G. Burton-Williams
Date: July 19, 2002
Re: Portal Hypertension Termination

Communication # 31

On November 29, 2001, the HALT-C steering committee voted to discontinue the Portal Hypertension Ancillary Study. A termination document has been prepared to ensure that patients who consented to participate in this study understand that it is no longer active. The document records that the principal investigator has discussed the Portal Hypertension Ancillary Study's termination with the consented patient. The termination document applies only to the sites that participated in the Portal Hypertension Ancillary study: UMASS, MGH, UMich, VCUHS. NERI will send paper copies of the termination document to those sites which had consented patients (UMich and VCUHS). The document is also available on the NERI website. Once, the termination document has been signed by the consented patient and the principal investigator, it should be placed with the consent forms in the patient's chart.