HALT-C Trial Q x Q

Sustained Virologic Responder Follow-up Ancillary Study:

Clinical Outcome

Form #763 Version A: 05/01/2008

Purpose of Form #763: This form is used to document the occurrence of clinical outcomes.

Outcomes in the HALT-C trial are expected progressions of liver disease. **The following nine outcome types require sites to complete a Clinical Outcome Form #763 and collect source documentation.** Please refer to Tables A and B of this document or the study protocol for complete definitions of each clinical outcome type.

1. Death from any cause
2. Development of hepatocellular carcinoma
3. CTP score of 7 or higher
4. Variceal hemorrhage
5. Ascites
6. Spontaneous bacterial peritonitis
7. Hepatic encephalopathy
8. Liver transplant
10. Development of presumed hepatocellular carcinoma

When to complete Form #763: This form should be completed once for each type of clinical outcome event that the investigator determines definitely, probably, or possibly meets one of the nine clinical outcome definitions.

This form must be completed and sent to the Data Coordinating Center (DCC) for data entry, along with appropriate source documentation.

Send a copy of this form, along with copies of all source documents, within one week of notification of the clinical outcome. Per federal HIPAA guidelines, black out all identifying patient information, such as name and medical record number, and replace with the patient ID number (labels provided by the DCC may be used).

See the box below for address, phone, and fax numbers.

DCC Contact Information

Contact:	Kristin Snow
Phone:	(617) 923-7747 x292
Fax:	(617) 926-0144
E-mail:	ksnow@neriscience.com
Address:	HALT-C Data Coordinating Center New England Research Institutes 9 Galen Street Watertown, MA 02472

SECTION A: GENERAL INFORMATION

A1. Affix the patient ID label in the space provided.
- If the label is not available, record the ID number legibly.

A2. Enter the patient's initials exactly as recorded on the Trial ID Assignment form.

A3. Enter the date this form was completed using MM/DD/YYYY format.

A4. Enter the initials of the person completing the form.

SECTION B: CLINICAL OUTCOME

Please note, only one clinical outcome should be reported per form.

B1. Enter the numerical code that corresponds to the clinical outcome being reported. Choose a clinical outcome code number from the list on the form.

- If the clinical outcome is coded 1 for DEATH, also complete Section E of Form #763.
- If the clinical outcome is coded 2 for DEVELOPMENT OF HCC, also complete Section F of Form #763.
- If the clinical outcome is coded 8 for LIVER TRANSPLANT, also complete Section G of Form #763.
- If the clinical outcome is coded 10 for DEVELOPMENT OF PRESUMED HCC, also complete Section F of Form #763.

SECTION C: SOURCE DOCUMENTS

A source document is a part of a patient's medical record that serves to validate data entered on Form #763. Identifying information on any document (name of patient, site, or physician; medical record number; etc.) should be blacked out when preparing copies for the DCC. Patient ID labels provided by the DCC should be placed on each page. The site must mail or fax a copy of the Form #763 and any required or supportive source documentation to the DCC.

The nine clinical outcomes have **required** source documentation that must be collected. Many have optional **supportive** source documentation that may be collected if available. Please refer to Tables A and B of this document or for information on required and supportive source documentation.

C1. Using the source document code list on the right side of Form #763, specify the source documents available to verify this clinical outcome.

C1a. For documents not included on this list, use code 99, and specify in the space provided. Fifty characters (including punctuation and spaces) are provided.

C1b. Enter the date on the source document.

SECTION D: DESCRIPTION

D1. Provide a written description of the clinical outcome, including the clinical events and procedures that lead to the diagnosis of the clinical outcome. 750 characters (including punctuation and spaces) are provided.

IF REPORTED OUTCOME IS DEATH, COMPLETE SECTION E.

IF REPORTED OUTCOME IS DEFINITE HCC OR PRESUMED HCC, COMPLETE SECTION F.

IF REPORTED OUTCOME IS LIVER TRANSPLANT, COMPLETE SECTION G.

FOR OTHER TYPES OF OUTCOMES, FORM IS COMPLETE.

SECTION E: COMPLETE ONLY IF REPORTED OUTCOME IS DEATH

Note: If additional information on an outcome of death becomes available, edit this section to reflect these changes and send source documentation as instructed on page 1.

E1. Enter the date of death using MM/DD/YYYY format.

E2. Record how information regarding the circumstances surrounding the patient's death was primarily obtained.

- Circle 1 for YES or 2 for NO for each question E2.
- You may answer YES to more than one question.

E3. Indicate if the Death Certificate is available.

- If the Death Certificate is available, circle 1 for YES and continue to question E4.
  - File a copy of the Death Certificate with the patient's records.
  - A copy of the Death Certificate should be sent to the DCC. Black out all identifying patient information, such as name and medical record number, and replace with the patient ID number (labels provided by the DCC may be used).
  - If the Death Certificate is not available, circle 2 for NO.

- If it is not possible to obtain a copy of the death certificate from a hospital or the patient's family, a copy can often be obtained from the state or county clerk by filing a request for a copy of a public record. There may be a nominal fee for this request. If it is difficult to request checks from your institution, the DCC can issue a check. Please contact the DCC with the amount, the name to make the check out to, and the address to send the check.

E4. Record the cause(s) of death. If there is a death certificate, please record the cause(s) of death listed on the death certificate. If a death certificate cannot be obtained, or has been requested but no received, please record the cause(s) of death fro the hospital record or autopsy report. If there is no hospital record or autopsy report, record the cause(s) of death reported by any other source.

- Specify the cause(s) of death. Sixty characters (including punctuation and spaces) are provided for each possible cause.
- When data entering a form where there are less than 4 causes of death, enter the cause(s) of death, and then enter "-1" in the next available space to skip to question E5.

E5. Enter the classification of cause of death as determined by a HALT-C site Principal Investigator.

- Circle 1 for YES or 2 for NO for each question E5.
- "-8" may be entered for "Don't Know" if the Principal Investigator is unable to make a determination of YES or NO for any question D1a-D1f.
- You may answer YES to more than one question.

SECTION F: COMPLETE ONLY IF REPORTED OUTCOME IS DEFINITE OR PRESUMED HCC

F1. Record the date the patient first met the criteria for definite/presumed HCC (in patient where the diagnosis of HCC is based on 2 imaging tests, please enter the date of the second confirming test) using MM/DD/YYYY format.

F2. Indicate if the diagnosis of HCC was made on the basis of histology.
- If the HCC was diagnosed by histology. End of Section F.
- If the HCC was not diagnosed by histology, go to question F3.

F3. Indicate if the diagnosis of HCC was determined by the presence of a new hepatic lesionwith AFP >1000 ng/mL.
- If the HCC was diagnosed by the new lesion and AFP >1000 ng/mL. End of Section F.
- If the HCC was not diagnoses by the new lesion and AFP >1000 ng/mL, go to question F4.

F4. Indicate the method of diagnosis. Choose only one of the methods from the code list. If the method is not listed, enter 99.

SECTION G: COMPLETE ONLY IF REPORTED OUTCOME IS LIVER TRANSPLANT

G1. Record the date that the patient received his or her liver transplant in MM/DD/YYYY format.

G2. Was the patient diagnosed to have HCC prior to the transplant?
- If the patient was diagnosed with HCC prior to the transplant, circle "1", if no then circle "2", if unknown, circle "-8."

G3. Does the liver pathology report show HCC in the explant liver?
- If the pathology report showed HCC in the explanted liver, circle"1", if no then circle "2", if report not available, circle "3."

Table A. CLINICAL OUTCOMES: Definitions, Required and Supportive Source Documentation

CLINICAL OUTCOME	PROTOCOL DEFINITION	REQUIRED SOURCE DOCUMENTATION	SUPPORTIVE DATA / DOCUMENTATION
Death from any cause	Death from any cause. Death may or may not be related to liver disease.	Must have one of the following: ▪ Social Security Death Index printout ▪ Death certificate ▪ Autopsy report ▪ Notation in any medical record reporting details of death	Attempt to obtain medical record notations or written information from outside sources. Notation may pronounce date and time of death, details of death, signed by medical practitioner.
Development of hepatocellular carcinoma	Defined as *EITHER*: ▪ Histology showing HCC (from a biopsy, surgery, or autopsy) *OR* ▪ A new hepatic defect on imaging with AFP rising to >1000 ng/ml	Must have *EITHER*: Histology (one of the following): ▪ Liver biopsy report ▪ Pathology report ▪ Autopsy report *OR* AFP result *AND* one of the following showing new defect or abnormality: ▪ Liver U/S report ▪ Liver CT report ▪ Liver MRI report	
CTP score of 7 or higher	Follow CTP Scoring Protocol	Must have all of the following: ▪ Copy of Form #715 ▪ Chemistry lab reports for two visits (albumin, serum total bilirubin, prothrombin time) ▪ Ascites documents if applicable (see below) ▪ Encephalopathy documents if applicable (see below)	
Variceal hemorrhage	Gastrointestinal hemorrhage that is due to bleeding esophageal or gastric varices, based on an endoscopy showing *EITHER*: Direct evidence of variceal bleeding (bleeding varix, red wale sign), *OR* Moderate varices with no other site of bleeding identified *AND* historical evidence for clinically significant upper GI bleeding.	Must have the following: ▪ Endoscopy report showing evidence of active or recurrent bleed within 48 hours of episode	May have: ▪ Medical record notation documenting episode of hemoptysis or rectal bleeding ▪ CBC report showing decline in Hgb

Table A. CLINICAL OUTCOMES: Definitions, Required and Supportive Source Documentation

CLINICAL OUTCOME	PROTOCOL DEFINITION	REQUIRED SOURCE DOCUMENTATION	SUPPORTIVE DATA / DOCUMENTATION
Ascites	Any abdominal fluid that is *EITHER*: Is mild, moderate, or marked on U/S. (An U/S report of minimal fluid around the liver does not meet the definition) *OR* Is progressive on serial physical examinations, *OR* Requires diuretic therapy.	Must have physical exam note *AND* one of the following: ▪ Paracentesis lab report ▪ Liver U/S report ▪ Liver CT report ▪ Liver MRI report	May have: ▪ Medical record notation of fluid volume removed
Spontaneous bacterial peritonitis	Any episode of spontaneous ascitic infection diagnosed on the basis of *EITHER:* Elevated neutrophil count (>250/ml) in paracentesis fluid, *OR* Positive bacterial cultures and clinical diagnosis, in the absence of WBC availability.	Must have paracentesis fluid lab report indicating one of the following: ▪ Elevated neutrophil count (>250/ml) ▪ (+) bacterial cultures	May have: ▪ Lab report of (+) blood culture ▪ Medical record notation ▪ Lab report of CBC showing an elevated WBC
Hepatic encephalopathy	Any mental status alteration that is due to portosystemic encephalopathy *EITHER*: Occurring during a provoked episode (GI bleeding, diuretics, usual sedative doses), *OR* Occurring spontaneously	Must have Medical record notation indicating one of the following: ▪ Asterixis ▪ Clinical alteration in mental status with reversibility with therapy ▪ Two or more episodes of confusion consistent with encephalopathy	May have: ▪ Elevated ammonia level ▪ Prolonged Trails test
Liver transplant	Liver transplantation surgery for progression of liver disease	Must have one of the following noting transplant: ▪ Medical record notation ▪ Operative report ▪ Explant histology report	

Table A. CLINICAL OUTCOMES: Definitions, Required and Supportive Source Documentation

CLINICAL OUTCOME	PROTOCOL DEFINITION	REQUIRED SOURCE DOCUMENTATION	SUPPORTIVE DATA / DOCUMENTATION
Development of presumed hepatocellular carcinoma	A new discrete hepatic defect is shown on U/S, AND histology is not available, AND the AFP is <1000 ng/ml, AND one of the following characteristics is present: ▪ Two liver imaging scans indicate malignancy with characteristics of HCC ▪ A progressively enlarging lesion eventually associated with massive liver involvement and death ▪ A new hepatic defect with one characteristic scan and one of the following: o Increase in size over time o Increasing AFP	Must have: ▪ Liver U/S report AND ▪ AFP report with result <1000 ng/ml AND one of the following: ▪ Two liver imaging scans ▪ Liver U/S report showing progressively enlarging defect AND a death report ▪ One liver imaging report showing a new hepatic lesion with HCC characteristics AND one of the following: o Increase in lesion size over time o AFP report increasing to a level of >200 ng/ml and more than tripling baseline level.	May have: ▪ Diagnostic angiography performed prior to intra-arterial chemo-embolization AND a radiology report describing tumor characteristics Note: Liver imaging scans include: ▪ MRI ▪ Triphasic CT ▪ Angiography ▪ Lipidolol scan ▪ Liver spleen scan with gallium