HALT-C Trial Q x Q

Clinical Outcome

Form # 63 Version B: 10/01/2002

Purpose of Form #63: This form is used to document the occurrence of primary clinical outcomes, outcomes requiring permanent cessation of Trial medication, and presumed hepatocellular carcinoma.

Outcomes in the HALT-C trial are expected progressions of liver disease. **The following ten outcome types require sites to complete a Clinical Outcome Form #63 and collect source documentation.** The types with an asterisk require permanent cessation of study drug (if applicable). Please refer to Tables A and B of this document or Section I, Clinical Outcomes, Appendices 1A, 1B, and 1C of the Manual of Operations 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 at two consecutive study visits requiring Form #15
4. Variceal hemorrhage
5. Ascites
6. Spontaneous bacterial peritonitis
7. Hepatic encephalopathy
8. * Liver transplant
9. * Meets 1999 criteria for UNOS transplant Status 2b
10. Development of presumed hepatocellular carcinoma

When to complete Form #63: This form should be completed for an event that the investigator determines definitely, probably, or possibly meets one of the ten clinical outcome definitions.

- If the Outcomes Review Board has confirmed that a patient has already met the criteria for an outcome, the second instance of the same type of clinical outcome in the same patient should be reported as applicable to the site's IRB. This data is not being collected for analysis and no additional HALT-C forms need to be completed or data entered.

- If presence of hepatocellular carcinoma is the only qualification for a patient meeting the UNOS Status 2b criteria, a single Form #63 can be completed listing "Development of HCC" as the outcome.

Reporting procedures for Clinical Outcomes: This form must be data entered and then sent to the Data Coordinating Center (DCC), along with appropriate source documentation, within four weeks of notification. See the box on page 3 for address, phone, and fax numbers.

Sites must report outcomes that occur during the Lead-In Phase (W00 through W24), Responder Phase (W30 through W72), and the Randomization Phase (R00 and M09 through M54). Clinical outcome events may be reported at a study visit or between study visits.

Patients in the Randomized Phase of the trial who experience a clinical outcome are followed through M54 (if possible). Patients who have a clinical outcome during the Lead-In Phase or the Responder Phase are not eligible for randomization.

NOTE ON OTHER FORMS TO BE COMPLETED WHEN AN ADVERSE EVENT OCCURS:

- **Adverse Event Form #60** should be completed for every clinical outcome. The sole exception is CTP score of 7 or higher at two consecutive visits that, per the investigator, does not qualify as an adverse event.
- **Serious Adverse Event Report Form #61** should be completed only when the clinical outcome is a death due to any cause.
- **Death Report Form #64** should be completed only when the clinical outcome is a death due to any cause.
- **HCC Diagnosis Form #66** should be completed when a randomized patient first meets the criteria of definite or presumed HCC. If liver samples are available, these should be shipped to the DCC for Central Pathology review.
- **Liver Transplant Report Form #67** should be completed when the clinical outcome is a liver transplant.
- **Early Termination of Peginterferon alfa-2a Treatment Form #19** should be completed if the clinical outcome results in the premature permanent termination of Peginterferon alfa-2a.
- **Dose Adjustment Form #28** should be completed if the clinical outcome resulted in a Peginterferon alfa-2a dose change.
- **Early Termination from Trial Form #25** should be completed if the clinical outcome results in early termination of the patient's participation in the HALT-C Trial.

SECTION A: GENERAL INFORMATION

Note on dates:

- All dates in this section should be recorded using MM/DD/YYYY format.
- Enter the 2-digit number for the month in the first two spaces provided (i.e., January = "01", February = "02", etc.), the 2-digit number for the day of the month in the second two spaces provided, and the 4-digit number for the year in the final four spaces provided.

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.

B0. Adverse Event Form #60 should be completed for every clinical outcome. The sole exception is CTP score of 7 or higher at two consecutive visits that, per the investigator, does not qualify as an adverse event. In this instance, circle 2 for NO and skip to question B2. Otherwise, circle 1 for YES and continue to question B1.

B1. Enter the adverse event number from Form # 60, Adverse Event Report, question B1 that corresponds to this clinical outcome.

B2. 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, Form #63 is complete. Completion of Form #64 Death Report is sufficient for death outcomes.
- For all other clinical outcome codes, continue to Section C.

SECTION C: SOURCE DOCUMENTS

A source document is a part of a patient's medical record that serves to validate data entered on Form #63. Identifying information on any document (name of patient, site, or physician; medical record number; randomized treatment group) should be blacked out when preparing copies for the DCC. Patient ID labels provided by the DCC should be placed on each page. Within four weeks of data entering a Form #63, the site must mail or fax a copy of the Form #63 and any required or supportive source documentation to the DCC.

The ten 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 Section I, Clinical Outcomes, Appendices 1A, 1B, and 1C of the Manual of Operations for information on required and supportive source documentation.

C1. Using the source document code list on the right side of Form 63, 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.

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).

DCC Contact Information

Contact:	Kristin Snow
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Table A. CLINICAL OUTCOMES: Definitions, Forms to Complete, Required and Supportive Source Documentation

CLINICAL OUTCOME	PROTOCOL DEFINITION	FORMS TO COMPLETE	REQUIRED SOURCE DOCUMENTATION	SUPPORTIVE DATA / DOCUMENTATION
Death from any cause	Death from any cause. Death may or may not be related to liver disease.	Form #60 required Form #61 required Form #64 required Form #63 required if Screening Phase complete	Must have one of the following: ▪ 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	Form #60 required Form #63 required if Screening Phase complete	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 at two consecutive study visits where Form #15 is required	Follow CTP Scoring Protocol	Form #60 required (unless PI determines that the elevated CTP score does not qualify as an adverse event) Form #63 required if Screening Phase complete	Must have all of the following: ▪ Chemistry lab reports for two visits (albumin, serum total bilirubin, prothrombin time) ▪ Ascites documents if applicable (see below) ▪ Encephalopathy documents if applicable (see below)	Copy of two Form #15s

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CLINICAL OUTCOME	PROTOCOL DEFINITION	FORMS TO COMPLETE	REQUIRED SOURCE DOCUMENTATION	SUPPORTIVE DATA / DOCUMENTATION
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.	Form #60 required Form #63 required if Screening Phase complete	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
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.	Form #60 required Form #63 required if Screening Phase complete	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.	Form #60 required Form #63 required if Screening Phase complete	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

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CLINICAL OUTCOME	PROTOCOL DEFINITION	FORMS TO COMPLETE	REQUIRED SOURCE DOCUMENTATION	SUPPORTIVE DATA / DOCUMENTATION
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	Form #60 required Form #63 required if Screening Phase complete	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	Form #60 required Form #67 required Form #63 required if Screening Phase complete	Must have one of the following noting transplant: ▪ Medical record notation ▪ Operative report ▪ Explant histology report	
Meets 1999 criteria for UNOS transplant Status 2b	(a) Presence of a small hepatocellular carcinoma *OR* (b) CTP score of 10 or more *OR* (c) CTP score of 7 or more, *AND* any of the following: ▪ Documented unresponsive variceal hemorrhage ▪ Hepatorenal syndrome ▪ Occurrence of one episode of spontaneous bacterial peritonitis (SBP) ▪ Refractory ascites or hydrothorax unresponsive to treatment	Form #60 required Form #63 required if Screening Phase complete Note: Presence of a small hepatocellular carcinoma that is the ONLY qualification for a patient meeting the UNOS Status 2b criteria does not require a separate Form #63. In this instance, a single Form #63 can be completed listing "Development of HCC" as the reported outcome.	(a) See above for required documentation for development of HCC (b) and (c) See above for required documentation for CTP scores See Table B for definition and documentation of: ▪ Variceal hemorrhage ▪ Hepatorenal syndrome ▪ Spontaneous bacterial peritonitis ▪ Refractory ascites and hydrothorax	

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

CLINICAL OUTCOME	PROTOCOL DEFINITION	FORMS TO COMPLETE	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	Form #60 required Form #63 required if Screening Phase complete	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

Table B. UNOS 2B Definitions, Required and Supportive Source Documentation

UNOS STATUS 2B CRITERIA	PROTOCOL DEFINITION	REQUIRED SOURCE DOCUMENTATION	SUPPORTIVE DATA / DOCUMENTATION
CTP score of 7 *AND* Documented unresponsive variceal hemorrhage	Endoscopically confirmed variceal hemorrhage, requiring 2 or more units of RBC replacement that continues or recurs after a series of endoscopic therapies to ablate the varices, or endoscopically confirmed portal hypertensive gastropathy requiring 2 units of RBC replacement that continues or recurs. Either TIPS or other surgical shunt must be contraindicated or have failed	Must have endoscopy report showing evidence of active or recurrent bleed within 48 hours of episode *AND* Notations in the medical record must show *BOTH* of the following: ▪ Documentation of 2 units or more of RBC *AND* ▪ Bleeding did not respond to injection, ligation, TIPS or shunt, *OR* indication that TIPS was contraindicated	May have: ▪ Medical record notation documenting episode of hemoptysis or rectal bleeding ▪ CBC lab report showing decline in Hgb
CTP score of 7 *AND* Hepatorenal syndrome	Progressive deterioration in renal function, with no other etiology, rising serum creatinine to >1.5 mg/dl and one of the following: ▪ Urine volume <500 ml/day ▪ Urine sodium <10 mEq/L ▪ Urine osmolality divided by plasma osmolality >1	Must have renal panel of blood lab report (serum creatinine >1.5 mg/dl and rising) *AND* one of the following: ▪ Electrolytes of urine lab report (urine sodium <10 mEq/L) ▪ Notation of decreased urine output (<500 ml/day) ▪ Notation of hospitalization	May have: ▪ Urine osmolality lab report ▪ Medical record notation indicating no response to a fluid challenge ▪ Documented presence of ascites
CTP score of 7 *AND* One episode of spontaneous bacterial peritonitis	Any episode of spontaneous ascitic infection diagnosed on the basis of 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 report showing *EITHER*: ▪ Elevated neutrophil count (>250/ml) *OR* ▪ (+) bacterial cultures	May have: ▪ Lab report of (+) blood culture ▪ Medical record notation ▪ CBC lab report of elevated WBC

Table B. UNOS 2B Definitions, Required and Supportive Source Documentation

UNOS STATUS 2B CRITERIA	PROTOCOL DEFINITION	REQUIRED SOURCE DOCUMENTATION	SUPPORTIVE DATA / DOCUMENTATION
CTP score of 7 AND Refractory ascites unresponsive to treatment	Severe persistent ascites, unresponsive to diuretic therapy and salt restriction, requiring large volume paracentesis more frequently than every 2 weeks, TIPS is contraindicated or failed	Must have Medical record notation of one of the following: ▪ Unresponsiveness to diuretic therapy and salt restriction ▪ TIPS (or TIPS contraindicated) ▪ Requires large volume paracentesis more frequently than every 2 weeks *AND EITHER:* ▪ Paracentesis lab report showing serum:ascites albumin gradient ≥1.1 *OR* ▪ Imaging (one of the following): o Liver U/S report o Liver CT report o Liver MRI report	
CTP score of 7 *AND* hydrothorax unresponsive to treatment	Severe persistent hydrothorax unresponsive to diuretic therapy and salt restriction, requiring large volume paracentesis or thoracentesis more frequently than every 2 weeks, TIPS is contraindicated or failed	Must have Medical record notation of one of the following: ▪ Unresponsiveness to diuretic therapy and salt restriction ▪ TIPS (or TIPS contraindicated) ▪ Requires large volume paracentesis more frequently than every 2 weeks *AND* all of the following: ▪ CXR report ▪ Thoracentesis lab report showing serum:pleural fluid albumin gradient of ≥1.1 ▪ Imaging (one of the following): o Liver U/S report o Liver CT report o Liver MRI report	