HALT-C Clinical Outcomes

I. Introduction

The aim of the HALT-C trial is to determine the safety and efficacy of long-term interferon therapy in patients with Hepatitis C. In order to evaluate this aim, several outcome variables will be evaluated over the course of the trial.

II. Definition

The major clinical outcome variable in this study will be the progression of liver disease, as determined by the occurrence of events associated with liver disease progression. These events include primary outcomes, secondary outcomes, and other outcomes that require discontinuation of trial medication.

III. Types of Clinical Outcomes

A. Primary Outcomes

The major outcome variable, the progression of liver disease, will be assessed by the following eight primary outcomes:

1. Increase in fibrosis score by 2 points or more at year 2 or year 4 biopsy (determined by Central Pathology Review).

2. Death from any cause.

3. Development of hepatocellular carcinoma (HCC) based on *either*:
   a. Histology showing HCC (from a biopsy, surgery, or autopsy), *or*
   b. A new hepatic defect on imaging with an AFP rising to > 1,000 ng/ml.

4. CTP score of 7 or higher at two consecutive study visits (i.e., two visits where completion of CTP Score Form #15 is required).

5. Variceal hemorrhage defined as gastrointestinal hemorrhage that is due to bleeding esophageal or gastric varices, based on an endoscopy showing *either*:
   a. Direct evidence of variceal bleeding (bleeding varix, red wale sign), *or*
   b. Moderate varices with no other site of bleeding identified, plus historical evidence for clinically significant upper gastrointestinal bleeding.

6. Ascites defined as any abdominal fluid that is *either*:
   a. "Mild", "moderate", or "marked" on ultrasound. (Abdominal fluid that is "mild" or "barely detectable" on physical examination requires ultrasound confirmation of "mild", "moderate", or "marked" ascites. An ultrasound report of "minimal" fluid around the liver does not meet the definition), *or*
   b. Progressive on serial physical examinations, *or*
   c. Requires diuretic therapy.

7. Spontaneous bacterial peritonitis (SBP) defined as any episode of spontaneous ascitic infection diagnosed on the basis of *either:*
   a. Elevated neutrophil count (> 250/ml) in paracentesis fluid, *or*
   b. Positive bacterial cultures and clinical diagnosis, in the absence of WBC availability.

8. Hepatic encephalopathy defined as any mental status alteration that is due to portosystemic encephalopathy *either*:

a. Occurring during a provoked episode (GI bleeding, diuretics, usual sedative doses), *or*
b. Occurring spontaneously (without apparent cause).

B. Outcomes Requiring Permanent Discontinuation of Trial Medication

In addition, the following outcomes require permanent discontinuation of trial medication. For more details, see Section V.E on dose adjustments in the Adverse Event Section I-1 of this Manual of Operations.

1. Liver transplant

2. Hepatocellular carcinoma (HCC)

3. UNOS Status 2b as defined by the 1999 UNOS Transplant Criteria Meeting:
   a. Presence of a small hepatocellular carcinoma, *or*
   b. CTP score of 10 or more, *or*
   c. CTP score of 7 or more, plus any one of the following:
      - Documented unresponsive variceal hemorrhage, *or*
      - Hepatorenal syndrome, *or*
      - Occurrence of one episode of spontaneous bacterial peritonitis, *or*
      - Refractory ascites or hydrothorax unresponsive to treatment.

By these criteria, outcomes of onset of ascites, variceal hemorrhage, CTP score >7 at two consecutive study visits, and hepatic encephalopathy do not require discontinuation of trial medication. However, trial medication dosage may be modified or withheld if continuation is not in the patient's best interest, in the opinion of the investigator.

Randomized patients who stop receiving trial medication will continue to be followed at regular visit intervals for the duration of the trial, if possible. Patients who discontinue treatment during the Lead-In Phase will not be followed beyond the Week 24 visit except for follow-up on any unresolved adverse event.

C. Secondary Outcomes

The major outcome variable, the progression of liver disease, will also be assessed by the following five secondary outcomes:

1. Quality of life.
2. Serious adverse events.
3. Events requiring dose reductions.
4. Changes in fibrosis score from baseline at year 2 or year 4 biopsy (determined by Central Pathology Review).
5. Development of presumed hepatocellular carcinoma. Presumed HCC will be considered when a new discrete hepatic defect is shown on ultrasound, histology is not available, the AFP is <1000 ng/ml, and one of the following characteristics is present:
   a. Two other liver imaging scans (MRI, triphasic CT, angiography, lipidol scan, liver spleen scan with gallium) indicate malignancy with the following characteristics: hypervascularity, arterial to portal vein shunts, portal vein thrombosis near the defect, tumor in the portal vein.
   b. A progressively enlarging lesion starting as a new defect eventually associated with liver involvement and death.
   c. A new hepatic defect with one characteristic scan and one of the following:
      - Increase in size over time (doubling in diameter size, or tripling in diameter size if the initial size <1 cm when first discovered).

- An increasing AFP (values 3 months before or after the discovery of the defect by scanning) eventually rising to a level of >200 ng/ml and more than tripling the mean baseline value.

IV. Clinical Outcome Procedures

A. Forms to be completed

1. Form #63, Clinical Outcome

The following ten primary outcomes, secondary outcomes, and outcomes that require discontinuation of trial medication *require completion of a Clinical Outcome Form #63*. Other outcomes do not require a Form #63 (for example, fibrosis score changes).

- Death from any cause
- Development of hepatocellular carcinoma
- CTP score of 7 or higher at two consecutive study visits
- Variceal hemorrhage
- Ascites
- Spontaneous bacterial peritonitis
- Hepatic encephalopathy
- Liver transplant
- Meets 1999 criteria for UNOS transplant Status 2b
- Development of presumed hepatocellular carcinoma

The Clinical Outcome Form #63 may be used for all patients in any phase of the trial. For events that are identified during the Screening phase of the trial before the Baseline visit, completion of Form #63 is at the discretion of the Investigator.

Form #63 must be completed for any event that an Investigator determines definitely, probably, or possibly meets the definition of one of these ten clinical outcomes. The event may be reported at a study visit or between study visits.

Form #63 must be completed as completely as possible within one week of clinical center notification of an event. Within four weeks of occurrence of a suspected clinical outcome, the clinical center must complete Form #63, and mail or fax a copy of the form and copies of collected source documentation to the DCC.

A separate Form #63 is completed and data entered for *every* suspected clinical outcome. For example, if a patient experienced ascites and encephalopathy resulting in a CTP score greater than 10, three Clinical Outcome Forms must be completed. The sole exception to this rule is:

- Presence of a small hepatocellular carcinoma that is the ONLY qualification for a patient meeting the UNOS Status 2b criteria. In this instance, a single Form #63 can be completed listing “Development of HCC” as the reported outcome.

2. Form #60, Adverse Event Report

Clinical outcomes are customarily considered adverse events. For information on reporting and grading adverse events, see Manual of Operations Section I-1: Adverse Events.

An Adverse Event Report Form #60 should be completed and data entered for *every* suspected clinical outcome. The sole exception to this rule is:

- CTP score of 7 or higher at two consecutive study visits that an investigator determines the event does not meet the adverse event definition. For example, an investigator may decide that an elevated CTP score resulting from mildly abnormal laboratory test results does not qualify as an adverse event.

3. Form # 61, Serious Adverse Event Report

The Serious Adverse Event Report Form #61 is completed and data entered *only* when the clinical outcome is a death from any cause. Note that deaths also require a Clinical Outcome Form #63, an Adverse Event Form #60, and a Death Report Form #64.

The Serious Adverse Event Form #61 is *not* completed when any other suspected clinical outcome has occurred. This is because a clinical outcome is considered a progression of the patient's existing liver disease and not related to study medication.

A Serious Adverse Event Form #61 must be completed and faxed within 24 hours of notification of a death from any cause. The DCC will send a fax or email confirmation upon receipt of notification of the death. Any patient death must also be reported via telephone to the DCC within 24 hours of site notification to:

Margaret Bell, RN
New England Research Institutes Inc.
9 Galen Street
Watertown, MA 02472
Phone: (617) 923-7747, x522
Fax: (617) 926-0144
Email: mbell@neri.org

4. Form #64, Death Report

The Death Report Form #64 is filled out when the clinical outcome is a death from any cause. The Death Report Form must be completed, data entered, and faxed to the DCC when all available source documents have been collected. Note that deaths also require a Clinical Outcome Form #63, an Adverse Event Form #60, and a Serious Adverse Event Form #61.

5. Form # 67, Liver Transplant Report

The Liver Transplant Report Form #67 is filled out when the clinical outcome is a liver transplant. Note that a liver transplant also requires a Clinical Outcome Form #63 and an Adverse Event Form #60.

6. Form # 66, HCC Diagnosis

The HCC Diagnosis Form #66 records the diagnosis of HCC and the characteristics of the tumor.

B. Clinical Outcome Source Documentation

A source document is a part of the patient's medical record that serves to validate data entered on Study form. For ten of the clinical outcomes, collection of specific source documentation is required. For some of these ten clinical outcomes, additional supportive documentation may also be collected. All source documents must be kept in the patient's chart. See Appendices A and B for specific details on required and supportive source documentation for each outcome type.

Identifying information on any document (name of patient, site, or physician; medical record number; and randomized treatment group) should be blacked out and replaced with the patient study ID number when preparing copies for the DCC. Patient ID labels provided by the DCC should be placed on each page.

Within four weeks of occurrence of a suspected clinical outcome, the clinical center must send a copy of the Clinical Outcome Form #63, with blacked out copies of required and supportive source documentation to:

Kristin Snow
New England Research Institutes Inc.
9 Galen Street
Watertown, MA 02472
Phone: (617) 923-7747, x292
Fax: (617) 926-0144
Email: ksnow@neri.org

C. Source Documentation Collected by Clinical Center (refer to Appendix A for details)

1. Death from any cause
   The required source documentation includes some or all of the following: death certificate, autopsy report, notation in any medical record (hospice, nursing home, hospital) reporting details of death.

2. Development of hepatocellular carcinoma
   The required source documentation includes some or all of the following reports: liver biopsy, liver pathology, liver autopsy, liver ultrasound, liver CT, liver MRI, and AFP lab result.

3. CTP score of 7 or higher at two consecutive study visits
   The required source documentation for elevated CTP scores includes copies of the Form #15s and the following laboratory reports: albumin, serum total bilirubin, prothrombin time in INR units. If ascites and/or encephalopathy is present, additional Form #63s may be required for these events. See Appendix C for information on CTP scoring.

4. Variceal hemorrhage
   The required source documentation is an endoscopy report showing evidence of active or recurrent bleed within 48 hours of episode.

5. Ascites
   The required source documentation includes some or all of the following reports: physical examination, paracentesis, liver ultrasound, liver CT, liver MRI.

6. Spontaneous bacterial peritonitis
   The required source documentation is a laboratory report of paracentesis fluid showing evidence of elevated neutrophil count >250/ml and/or positive bacterial cultures.

7. Hepatic encephalopathy

The required source documentation is a notation in the medical record indicating asterixis, clinical alteration in mental status with reversibility with therapy, and/or two or more episodes of confusion consistent with encephalopathy.

8. Liver transplant
   The required source documentation includes some or all of the following reports: notation in the medical record, operative report, explanted liver histology report.

9. Meets 1999 criteria for UNOS transplant Status 2b
   The required source documentation includes some or all of the following depending on the criteria met: endoscopy report, medical record notation, hospitalization record, TIPS, paracentesis lab report, renal function and urine lab report, liver ultrasound, liver CT report, liver MRI report. Refer to Appendix B for specific details on documentation. See Appendix C for information on CTP scoring.

10. Development of presumed hepatocellular carcinoma
    The required source documentation includes some or all of the following reports: AFP, liver ultrasound, liver MRI, triphasic CT, angiography, lipidol scan, liver spleen scan with gallium, documentation of death.

V. Clinical Outcomes Reviews

A. Review of Clinical Outcomes by the Outcome Review Board

For adjudication of clinical outcomes, the Outcomes Review Board (ORB) reviews required source documentation to confirm that an event with a completed Clinical Outcome Form #63 is diagnosed in a standard format. Principal Investigators from all of the clinical centers will participate in the ORB. Three investigators will be assigned to the ORB on a rotating schedule (see Appendix D for ORB schedule).

1. Responsibilities of the Data Coordinating Center (DCC)

   a. The DCC will set up a rotating schedule of Principal Investigators to participate in the ORB. Members will serve a 6-month term for the first 2 years of the study. During the last 4 years, the membership terms will be 3 months. Membership will be staggered, with one member remaining on for an additional 2-3 months for continuity purposes.

   b. The DCC will ensure that the there is no identifying patient or trial medication information on the source documents.

   c. The DCC will send a fax or email confirmation to the clinical center upon receipt of the clinical Outcomes Forms and source documents.

   d. When a clinical outcome is reported, the DCC will work with the clinical center to ensure that the appropriate study forms are completed and data entered.

   e. The DCC will send the documents within one week of receipt to two of the three investigators who form the ORB at that time and to the Project Officer at the NIDDK.

   f. If the initial two ORB members do not reach the same conclusion, the DCC will send the documents within one week of receipt to the third ORB member or to Leonard Seeff of the NIDDK acting as the third ORB reviewer.

g. After the final ORB review, the DCC will data enter the Review of Clinical Outcome Form #65.

h. After the final ORB review, the DCC will notify the reporting site on the final status of the clinical outcome (i.e., outcome confirmed, outcome not confirmed).

2. Responsibilities of the Outcomes Review Board (ORB)

a. The members of the ORB will review documents sent from the DCC simultaneously without need for face-to-face meeting each time a clinical outcome is met.

b. ORB members should not review clinical outcomes from their own site.

c. The ORB will not review Ishak scores.

d. Conference calls will be scheduled each time a new member joins the ORB.

e. Each member of the ORB will complete the designated page of the Review of Clinical Outcome Form #65 and send to the DCC within one week of receipt.

f. If the initial two ORB members do not reach the same conclusion the following will occur:
- The documents will be sent by the DCC to the third ORB member or to Leonard Seeff of the NIDDK acting as the third ORB reviewer.
- The third ORB reviewer will communicate with the DCC and the clinical center as needed to obtain additional information. The decision of the third reviewer will be final.

B. Clinical Outcomes Committee

The Clinical Outcomes Committee, established to develop procedures for the appropriate documentation and reporting of clinical outcomes, will review all clinical outcomes. A Clinical Outcomes Report will be generated by the DCC on an annual basis. When the reports are generated, the Clinical Outcomes Committee will meet by conference call to review them. This information will then be presented to the Steering Committee. The Data Safety Monitoring Board will also review information and reports generated on all clinical outcomes.

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

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
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

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
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	