Follow-up Events (Adult)

General Instructions

The Follow-up Events form captures study specific events and outcomes. Complete the form when you become aware of one or more of the following events:

- death
- liver transplantation
- initial diagnosis of hepatocellular carcinoma (HCC), hepatic decompensation, or cirrhosis
- a new episode of HBsAg or HBeAg loss
- a new onset of ALT flare
- the patient is no longer participating in the cohort protocol

This form is to be completed at the time you learn of an event or when you determine that clinical criteria meet the study definition of an event. If you learn of more than one event at the same time, one event form may be used to capture information on more than one event.

Specific Instructions

Patient ID**:** Record the Patient ID in the top right hand corner.

Date of Form: Record the date (month/day/year) that the form is completed.

Events: Check each event being reported according to the study definitions provided below. Events should be reported as you become aware of them. More than one event can be reported on one form.

Death: The cause of death may or may not be related to liver disease. One of the following should be available:

- death certificate
- autopsy report
- medical record with details of death

It may be necessary to report some of this information in the opinion of the investigator if this information is not documented in a health record.

For a patient death,

i. Record the date of death (month/day/year).
ii. Record the cause of death. Refer to the most recent codebook. If the cause is not listed, record the code for "Other" and complete the specify field.
iii. Check "Yes", "No", or "Unknown" to indicate if hepatitis B was determined to be the primary cause of death.
iv. Check "Yes", "No", or "Unknown" to indicate if hepatitis B was determined to be a contributing cause of death.
v. Check "Yes", "No", or "Unknown" to indicate if the death was determined to be due to a complication of therapy for hepatitis B.

Liver transplant: Orthotopic or living donor liver transplantation. One of the following must be available to confirm transplantation:

- Medical record notation
- Operative report
- Explant histology report

If the patient underwent liver transplantation,

i. Record the date of transplantation (month/day/year).
ii. Record the indication for transplant. Refer to the codebook for the list of reasons. If the reason is not listed, indicate "Other" and complete the specify field.
iii. Incidental HCC: check "Yes" or "No" to indicate if incidental HCC was found on explant. If yes, report the HCC on this event form and then complete the HCC form.

A liver tissue sample from the explanted liver should be obtained when possible.

No additional protocol follow-ups are completed once a patient receives a liver transplant.

Hepatocellular carcinoma (HCC):

Report only the initial diagnosis of HCC.
Confirmation of diagnosis must be made by histology provided by one of the following reports:

- Liver biopsy
- Pathology
- Autopsy

OR in the absence of histological evidence, the diagnosis may be made with an AFP lab result and the results from appropriate imaging test(s) as determined by current AASLD guidelines:

- Nodules < 1 cm found on surveillance will be followed with ultrasound at intervals of 12-24 weeks until a diagnosis of HCC is made or no growth is seen over 2 years.
- Nodules equal to 1 cm or between 1 to ≤ 2 cm will be investigated further with dynamic studies, such as contrast ultrasound, triphasic CT or MRI with contrast. Two studies must agree with the appearance of HCC, such as hypervascularity with washout in the venous phase, before a diagnosis is determined.
- If the nodule is > 2 cm and has the typical features on a dynamic imaging technique or AFP > 200 ng/ml, a diagnosis of HCC may be made.
- If these conditions are not met, a biopsy may be performed. Biopsy slides will be collected at the time of diagnosis or surgery/transplant.

If yes, record the date of diagnosis (month/day/year) and complete the HCC Form.

Hepatic decompensation:

Report only the initial diagnosis of hepatic decompensation.
The diagnosis of hepatic decompensation is defined as the presence of any of the following:

Ascites: Defined as an excess of fluid in the peritoneal cavity that is mild, moderate or marked on ultrasound (ultrasound report of minimal fluid around the liver does not meet the definition) or is progressive on serial physical examinations or requires diuretic therapy.

Hepatic hydrothorax: ascites associated pleural effusion.

Medical record must indicate the presence of ascites or diuretic usage and one of the following:

- Paracentesis lab report
- Liver ultrasound report
- Liver CT report
- Liver MRI report

Variceal bleeding: Defined as GI bleeding from varices present in the esophagus or stomach based on an endoscopy showing either:

- Direct evidence of variceal bleeding (bleeding varix, red wale sign)
- Moderate varices with no other site of bleeding identified and historical evidence for clinically significant upper GI bleeding.

Portal hypertensive bleeding: gastrointestinal bleeding associated with portal hypertension.

Medical record must include an endoscopy report showing evidence of active or recurrent bleed within 48 hours of an episode.

Hepatic encephalopathy: Characterized by recurrent disturbances of consciousness, impaired intellectual function, neuromuscular abnormalities, metabolic slowing on EEG and elevated serum ammonia levels. Symptoms include changes in mental state, consciousness, behavior and personality, decrease in performance of simple self-care tasks, and muscle spasms or rigidity. Also known as portal-systemic encephalopathy.

Medical record must indicate one of the following:

- Asterixis
- Clinical alteration in mental status with reversibility with therapy
- Two or more episodes of confusion consistent with encephalopathy

CTP (Child-Turcotte-Pugh) score ≥ 7:

CTP score is calculated using the algorithm below.

		Number of points		
Items	**Units**	**1**	**2**	**3**
Serum albumin	g/dL	>3.5	2.8-3.5	<2.8
Serum total bilirubin No Gilbert's Syndrome No hemolytic diseases Not receiving Ribavirin	mg/dL	<2.0	2.0-3.0	>3.0
Serum total bilirubin Presence of Gilbert's Syndrome Hemolytic disorder such as patients receiving Ribavirin*	mg/dL	<4.0	4.0-7.0	>7.0
INR		<1.7	1.7-2.3	>2.3
Ascites		None	Mild^	Severe‡
Encephalopathy		None	Mild^	Severe‡

Note that if, in the opinion of the investigator, the patient has Gilbert's syndrome or a hemolytic disorder (e.g., patients receiving ribavirin) the level of the serum total bilirubin may be increased to as high as 3.99 mg/dL without considering the total bilirubin to be sufficiently elevated for the patient to receive a score of 2 in the CTP scoring system.

^ Mild means readily controlled by standard medical therapies.

‡ Severe means difficult to control or uncontrollable by optimal, maximally tolerated medical therapies.

The score is the sum of the scores for albumin, bilirubin, INR, ascites and encephalopathy (range 5-15)**.**

Class A = 5-6
Class B = 7-9
Class C = 10-15

If yes, record the following items:

i. Date of diagnosis (month/day/year). If any piece of the date is not known, record "Unk" for that piece.
ii. Evidence: check all that apply to report the evidence used to make the diagnosis of HCC.

The HCC form should be completed when a patient is first diagnosed with HCC.

Cirrhosis:

Report only the initial diagnosis of cirrhosis.
The diagnosis of cirrhosis must be confirmed by liver histology or clinical criteria which consist of any evidence of hepatic decompensation (refer to definitions above) or the presence of at least two of the following:

Splenomegaly: also known as enlarged spleen and is swelling of the spleen beyond its normal size.

Nodular liver: documented by CT, MRI or liver ultrasound report.

Platelet count below 120,000/mm^3: result must be near to the time of diagnosis.

If yes, record the following

i. Date of diagnosis (month/day/year). If any piece of the date is not known, record "Unk" for that piece.
ii. Evidence: check all that apply to report the evidence used to make the diagnosis of cirrhosis.

The protocol follow-up schedule does not change for patients diagnosed with cirrhosis however, patients diagnosed with cirrhosis should be followed according to the current AASLD guideline for surveillance and early detection of HCC, consisting of ultrasonographic examination every 24 weeks and AFP tests.

HBsAg loss:	Check if a HBsAg (hepatitis B surface antigen) result was previously positive and a subsequent HBsAg test result is negative. If yes, record the following i. Date (month/day/year) of the first undetected HBsAg test result. ii. Date (month/day/year) of the last positive HBsAg test result. The Special Visit form should be completed at 12 and 24 weeks following the diagnosis of HBsAg loss, when the patient returns for evaluation.
HBeAg loss:	Check if a HBeAg (hepatitis B e antigen) result was previously positive and anti-HBe (hepatitis B e antibody) negative and a subsequent HBeAg result is negative. If yes, record the following i. Date (month/day/year) of the first undetected HBeAg test result. ii. Date (month/day/year) of the last positive HBeAg test result. The Special Visit form should be completed at 12 and 24 weeks following the diagnosis of HBeAg loss, when the patient returns for evaluation.
ALT flare:	Check if this is the initial ALT test result meeting the definition of ALT flare, defined as ≥ 300 IU/L in males and ≥ 200 IU/L in females. If yes, record the date of diagnosis (month/day/year). The Special Visit form should be completed when the patient returns for evaluation. Follow the unscheduled follow-up schedule identified in the protocol until the flare resolves. Complete the Flare Resolution form when the flare is considered to be resolved.
End of study participation:	Check if the patient will no longer participate in the cohort protocol for any reason other than death or liver transplantation, e.g. enrolled in a HBRN treatment trial, moved outside of HBRN network, lost to follow-up, etc. If yes, record the following i. Date (month/day/year) of the last successful contact by telephone, in-person visit, etc. ii. Reason the patient will no longer be participating in the cohort protocol. Refer to the codebook for the list of reasons. If the reason is not listed, indicate “Other” and complete the specify field. Follow the lost to follow-up procedure and complete the lost to follow-up checklist before reporting that the patient is lost to follow-up.