The following clinical events will be reviewed by the Adjudication Committee:

ALT flare	Hepatocellular carcinoma
Acute HBV	HBe/sAg loss
Cirrhosis	Liver transplantation
Hepatic decompensation	Death

The Adjudication Committee will:

1) confirm that the event occurred and the etiology if applicable
2) date of onset (or diagnosis) of the event

Information collected on the data forms will be provided to the Adjudication Committee. Some of the events will require supporting documentation obtained from the medical record or recorded on a worksheet, in addition to the information reported on the data forms. The supporting documents should be maintained in the participant's study chart. The suggested additional supporting documentation is listed below for each event. Events are adjudicated using local tests and labs.

ALT flare and Acute HBV (worksheet required)

Adult ALT Flare Definition: Serum ALT greater than or equal to 10 times the upper limit of normal corresponding to ≥ 300 IU/L in males or ≥ 200 IU/L in females.

Pediatric ALT flare definition:

- ALT test result ≥ 600 IU/L in males and ≥ 550 IU/L in females 6 months - 18 months of age
- ALT test result ≥ 400 IU/L in males and ≥ 350 IU/L in females >18 months - <18 years of age

Acute HBV:

- ALT flare: complete the ALT flare worksheet after the ALT flare has resolved and submit materials related to the flare
- Acute HBV: complete the ALT flare worksheet after the acute episode has resolved and submit materials related to the acute episode.
- Complete adjudication documentation for HBe/sAg events after HBe/sAg loss is confirmed (by negative results 12 and 24 weeks after initial negative result)

Probable etiology of flare / Documentation

Reactivation of hepatitis B - Increase in HBV DNA during flare

Etiology Code	Description
1	Spontaneous – by exclusion. HBV DNA before and during flare.
2	Upon withdrawal of antiviral therapy - Name of antiviral(s), start and stop date, HBV DNA end of Rx and during flare
3	Associated with immunosuppressive therapy (including DAAs) – Name of immunosuppressive medication(s), start and stop date, HBV DNA end of therapy and during flare
4	Progression of immunodeficiency – CD4, HIV RNA, HBV DNA just before and during flare, HAART regimen
5	Transition from IT to IA phase

Immune clearance of hepatitis B - Decrease in HBV DNA/HBeAg loss/HBsAg loss during flare

Etiology Code	Description
9	Unsuccessful attempt at immune clearance: Fails to achieve HBeAg seroconversion or HBsAg clearance despite a decrease in HBV DNA. Often accompanied by rebound increase in HBV DNA. HBV DNA and HBeAg/HBsAg before, during, and after flare
10	Spontaneous – by exclusion. HBV DNA and HBeAg/HBsAg before, during, and after flare
11	Antiviral therapy induced – Name of antiviral(s), start and stop date, HBV DNA/HBeAg/HBsAg before, during, and after flare

12	Immune reconstitution – HBV DNA, CD4 and HIV RNA just before and during flare, HAART regimen and start date
13	Withdrawal of antiviral therapy with flare and seroconversion – Name of antiviral(s), start and stop dates, HBV DNA and HBeAg/HBsAg before, during, and after flare

ALT Flare- No change in HBV DNA during flare

Etiology Code	Description
16	No change in HBV DNA before, during and after flare.

Drug-induced – recent addition of drugs (prescribed or over the counter) or herbals, or increase in alcohol consumption

Etiology Code	Description
20	Idiosyncratic. HBV DNA before and during flare, name of any and all potentially hepatotoxic medication(s)/herbals started in the previous 6 months, start and stop dates
21	Direct toxic. HBV DNA before and during flare, names of direct hepatotoxins taken in the month before the flare, start and stop dates and doses.
22	Alcohol – average number of drinks/day for 6 months before flare
23	Acetaminophen

Superimposed liver disease or infection – labs (date and result) and, if available, biopsy (date and result)

Etiology Code	Description
30	HAV – IgM anti-HAV or total anti-HAV (before and during flare)
31	HDV – Anti-HDV (before and during/after flare), or IgM anti-HDV, or HDV RNA, or liver biopsy with staining for HDAg
32	HCV – anti-HCV (before and during/after flare), HCV RNA
33	HEV – IgM anti-HEV or HEV RNA or IgG anti-HEV (before and during/after flare).
34	Autoimmune hepatitis – titers of antinuclear antibody, anti-smooth muscle antibody, anti-LKM, globulin levels (total protein-albumin), and, if available, liver biopsy or documented response to corticosteroid therapy (dates of starting and doses)
35	Other superimposed liver disease or infection

Other

Etiology Code	Description
40	Other etiology of flare
41	Unknown
42	Acute hepatitis
43	HBV related but inadequate information to determine a specific etiology

Cirrhosis (worksheet required)
Definition: In the absence of histological diagnosis, cirrhosis is defined as:

- Any one of the following
  - Presence of ascites or hepatic hydrothorax
  - Variceal or portal hypertensive bleeding
  - Hepatic encephalopathy
  - Child-Turcotte-Pugh (CTP) score of 7 or above

OR in the absence of hepatic decompensation

- Any two of the following (in the absence of another explanation)
  - Splenomegaly (documented by imaging)
  - Nodular liver (as shown by imaging)
  - Platelet count below 120,000/mm^3

Documentation

1. Liver biopsy – date, biopsy report, slides
2. Ascites – US/CT/MRI (date, report, finding of more than minimal fluid), detection on physical exam, require treatment (diuretics – medication list, start date and name, or paracentesis – date and volume drained, clinic note, hospital note or procedure note)
3. Variceal bleeding – hospital note documenting admission for GI bleeding, endoscopy report with direct evidence of variceal bleeding or moderate/large varices with no other source of bleeding plus evidence of drop in hemoglobin
4. Hepatic encephalopathy – hospital note documenting admission for encephalopathy and improvement with treatment (lactulose, antibiotics), detection on physical exam, require treatment, start date of medications used to treat encephalopathy
5. CTP score ≥7 – date and results of albumin, INR, bilirubin + presence or absence of ascites / encephalopathy on the same day
6. If no histology and no decompensation – need date and imaging report documenting splenomegaly and/or nodular liver, and platelet count

Hepatic decompensation (worksheet required) – documentation as above
Definition: hepatic decompensation will be defined by any of the following events:

- Ascites or hepatic hydrothorax
- Variceal or portal hypertensive bleeding
- Hepatic encephalopathy
- Child-Turcotte-Pugh (CTP) score of 7 or above

Hepatocellular carcinoma (HCC)
Definition: Per AASLD guidelines
Documentation:

1. Histology – date, report, and slides or
2. Dynamic imaging – CT/MRI report from which diagnosis was made and just prior (if available)
3. AFP

Death (cause of death)
Documentation:

1. Hospital notes, death certificate (if obtainable), or communication with patient's family or PCP?
2. Was hepatitis B the primary cause of death?
3. Was hepatitis B a contributing cause of death?
4. Did the patient die as a complication of therapy of hepatitis B?

Antigen loss: e or s
Documentation:

1. Lab report showing last time HBe/sAg positive and first two consecutive HBe/sAg negative
2. Lab reports from 12 and 24 weeks after first time HBe/sAg negative to confirm loss (or two consecutive negative results regardless of time interval)

Liver transplantation (reason for transplant)
Documentation:

1. Copy of transplant surgery procedure note
2. Explant pathology report

Process

- Clinical center personnel will complete the Adjudication Coversheet, an adjudication worksheet (when applicable), and provide appropriate source documentation, with patient identifiers redacted. This information sent to the DCC.
- Adjudication materials should be submitted to the DCC when all of the necessary information is available. For example, adjudication materials for an ALT flare should be submitted following resolution of the flare when the data forms, adjudication worksheet, and supporting documents are complete.
- The adjudication committee will consist of 6 clinical center investigators (4 adult and 2 pediatric), an NIDDK representative, and one representative from the DCC as ex-officio. The clinical center investigators will rotate throughout the course of the study
- The DCC will prepare adjudication packages for committee members to review as the events are reported.
- An investigator will not review a case from his/her clinical center.
- Two investigators will review each event and if there is an inconsistent determination between the site investigator and the adjudicators or between the adjudicators, the event will be reviewed by the entire committee or NIDDK. These events will be adjudicated by majority vote or consensus.