Adult Immune Active (IA) Trial Treatment Discontinuation and Reinitiation Process Manual of Operations

6.4.1 Review criteria for discontinuing treatment and resumption of treatment and post treatment follow up schedule

At the week 180 visit, the scheduled visit prior to the visit at which eligible participants are scheduled to discontinue treatment, a study physician will review the rationale for antiviral withdrawal, criteria for treatment discontinuation, potential benefits and risks, criteria for resuming treatment, and the post treatment follow up schedule with the participants. The study PI will document this discussion in the participant's record. The participant will be provided with a fact sheet that will be reviewed by a study physician and a signed copy maintained in the study record. Participants should be reminded to bring all remaining study medication to the next visit (week 192). Blood will be drawn for qualitative HBeAg, anti-HBe, and HBsAg testing so results are available at week 192. Eligibility to discontinue treatment will be reconfirmed by the study PI on week 192.

6.5.1 Eligibility criteria for discontinuing treatment at week 192 (participants must meet all criteria)

Participants will be discontinued from treatment if they meet all of the following criteria as determined based on laboratory results at the week 180 visit and any additional test results and clinical assessment up until the week 192 visit:

1. HBV DNA <1000 IU/mL for the previous 24 weeks (i.e. starting at or before week 156 and continuing through week 180).
2. No cirrhosis (Ishak score 5 or 6) on baseline biopsy – from the central pathology read
   NOTE: the Ishak score from the central pathology read should be used. If a score from the central read is not available the score from the local read may be used.
3. Normal indices of liver function (CTP =5), albumin ≥3.8 g/dL, INR ≤1.3, direct bilirubin ≤0.5 mg/dL
4. No clinical evidence of decompensation
5. No clinical or radiologic evidence of portal hypertension
6. Platelet count ≥120,000/mm^3
7. HBeAg-negative at baseline visit and confirmed at week 180, or HBeAg-positive at baseline visit with HBeAg loss at or before week 144 and confirmed at week 180. In either situation, there can be no HBeAg positive result at or after week 144.
8. HBsAg-negative (regardless of anti-HBe status), or if HBsAg-positive, HBeAg-negative and anti-HBe-positive at week 180

Participants who do not meet criteria for discontinuing treatment will continue treatment with tenofovir DF until Week 240. Tenofovir DF for the period Week 192 to Week 240 will be provided by the study. Follow up visits and testing will continue every 12 weeks (204, 216, 228) to week 240. If tenofovir DF will be continued beyond Week 240, medication must be obtained per standard of care.

Participants who meet criteria for discontinuing treatment but choose to continue treatment will have follow-up visits and testing per the schedule for participants who discontinue treatment. No study medications (Tenofovir DF) will be provided beyond Week 192 and any antiviral therapy must be obtained per standard of care.

6.6 Post Treatment assessments (Appendix 4)

1. Outpatient visits will occur at weeks 196, 200, 204, 208, 212, 216, 228, and 240 for participants in both treatment groups.
2. Laboratory testing (liver panel) plus telephone assessment can replace an outpatient visit at weeks 208 and 212 if ALT at the preceding assessment (week 204 and week 208, respectively) is <300 U/L for men or <200 U/L for women and bilirubin is normal (total bilirubin <1.5 mg/dL or direct bilirubin <0.5 mg/dL)
3. Medical history and physical exam at week 240.
4. Clinical evaluation at weeks 196, 200, 204, 208, 212, 216, and 228.
5. Assessment of adverse events and concomitant medications at each visit.
6. Questionnaires (quality of life, depression assessment, fatigue, and health behaviors) at week 240.
7. Symptom questionnaire at each visit.
8. CBC including platelets, alkaline phosphatase, albumin, total protein, and creatinine at week 240.

9. Renal panel (creatinine, calculated creatinine clearance, phosphate, blood urea nitrogen, and calcium) at each study visit for participants who are on Tenofovir
10. Hepatic panel (ALT, AST, albumin, total protein, alkaline phosphatase, total and direct bilirubin) at each visit.
11. Urinalysis at week 240.
12. PT/INR at weeks 196, 200, 204, 216, and 240.
13. Blood samples for serum/plasma at each outpatient visit.
14. Qualitative HBsAg, HBeAg, and anti-HBe at weeks 216 and 240.
15. Anti-HBs and antiviral drug resistance testing at week 240.
16. HBsAg quantificationat weeks 204, 216, 228, and 240.
17. HBeAg quantification at weeks 204, 216, 228, and 240.
18. HBV DNA at each outpatient visit
19. Ultrasound exam (If clinically indicated, per AASLD guidelines, done as standard of care) at week 240.
20. Fibroscan (if available and obtained at, or since, the week 180 visit but not later than the week 192 visit) at week 240.

6.14.2. Criteria for treatment reinitiation in the Post-Treatment Follow up Period

Tenofovir DF will be restarted for any one of the following:

- Any one of the three criteria: INR ≥1.3, total bilirubin ≥3.0 mg/dL or direct bilirubin ≥1.0 mg/dL, regardless of HBV DNA or ALT level.
- Any clinical decompensation, regardless of HBV DNA or ALT level.
- HBV DNA ≥10,000 IU/mL and ALT >1000 U/L (male or female) (i.e. only one ALT value >1000 U/L is needed to qualify).
- HBV DNA ≥10,000 IU/mL and ALT ≥300 U/L for males, ≥200 U/L for females. A total of one HBV DNA ≥10,000 IU/mL and any three ALT values ≥300 U/L (male) or ≥200 U/L (female) over the 4-week (or longer) time frame are needed to qualify. Treatment will be resumed if the third ALT remains ≥300 U/L (male) or ≥200 U/L (female).
- HBV DNA ≥10,000 IU/mL and ALT ≥150 U/L for males or ≥100 U/L for females. A total of one HBV DNA ≥10,000 IU/mL and any three ALT values ≥150 U/L (male) or ≥100 U/L (female) over the 12 week (or longer) time period are needed to qualify. Treatment will be resumed if the third ALT remains ≥150 U/L (male) or ≥100 U/L (female).
- HBsAg-positive and HBeAg-positive at week 192.
- HBsAg-positive, HBeAg-negative, and anti-HBe-negative at week 192

NOTE:

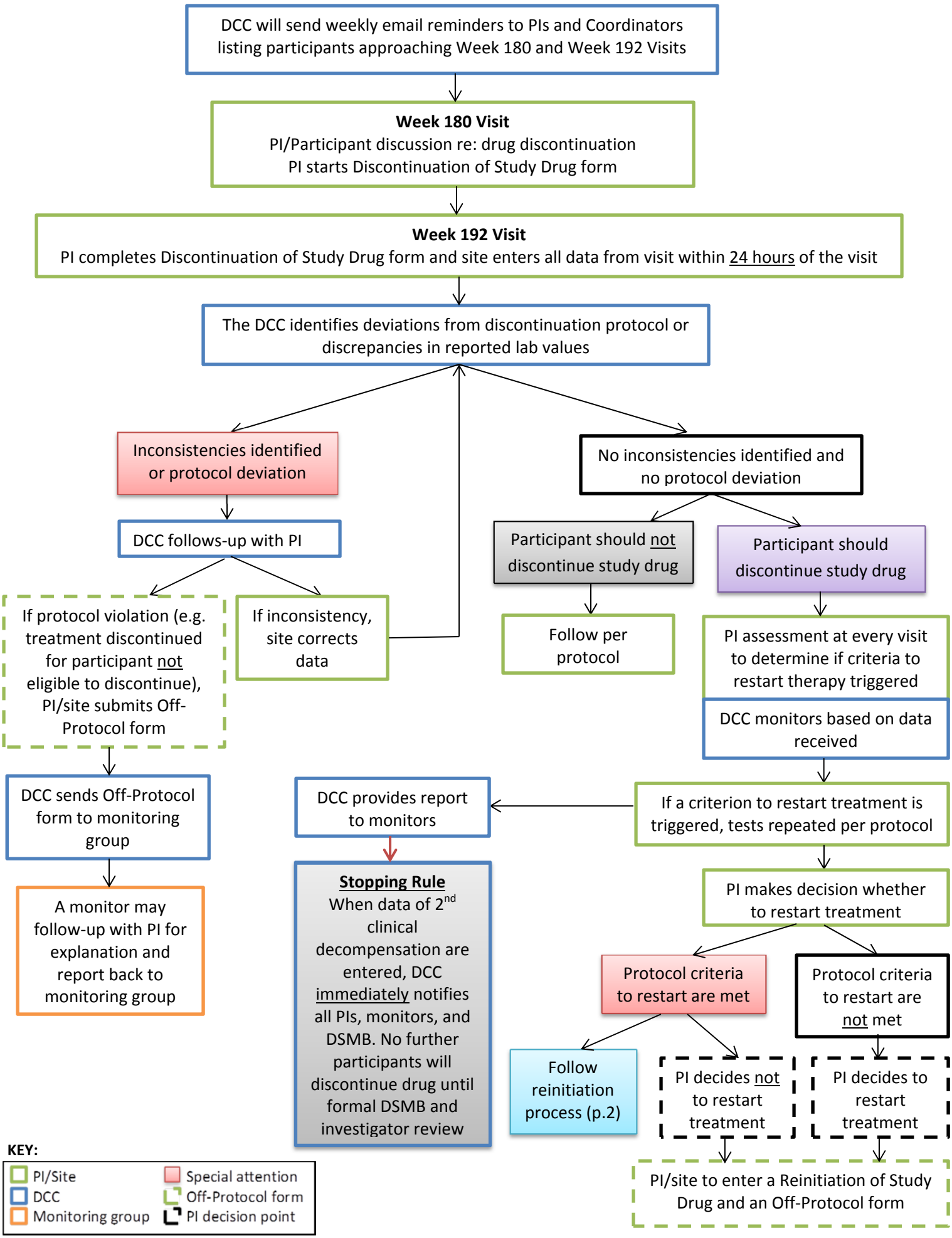
- **Initial HBV DNA test result (≥ 10,000 IU/mL) should be from the <u>HBRN Central Lab</u> at the University of Washington**
- **Initial and repeat ALT tests are per local lab**
- **Obtain at least 1mL serum samples for storage at the time of the repeat visits and then ship these aliquots to the <u>NIDDK Repository</u> per the usual procedure. Serum aliquots for the repeat HBV DNA tests will be selected by the DCC and batch shipped to the UWash Central Lab for HBV DNA testing.**
    - **Repeat HBV DNA tests do not need to be performed in real-time at the UWash lab when ALT tests are repeated, as the repeat HBV DNA results are not needed to determine if a HBV DNA and ALT criteria is met**

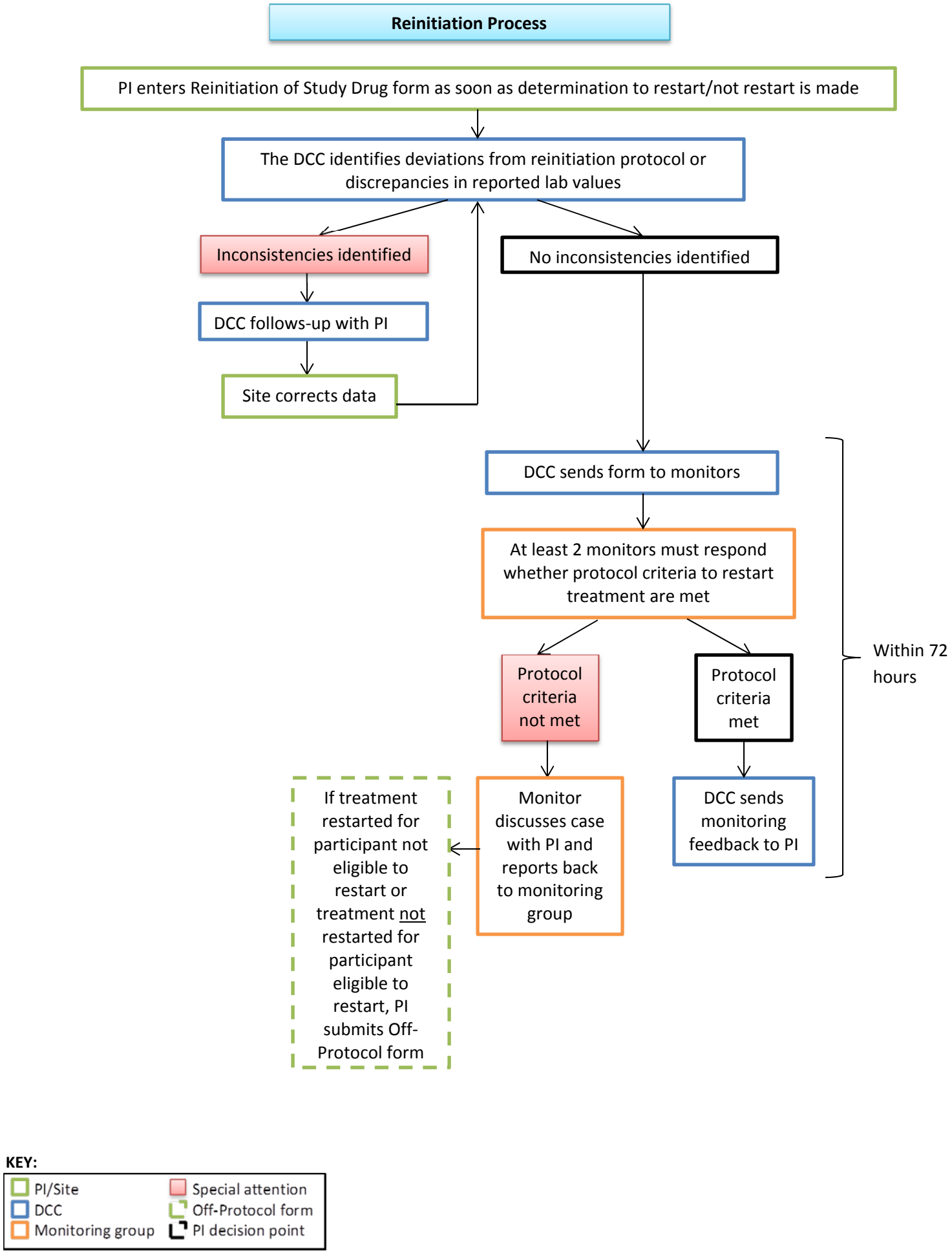
9.1 Data and safety monitoring plan

<u>Stopping rules during treatment discontinuation phase (Weeks 192 to 240)</u>

The following has been agreed upon by the clinical investigators

1. If >1 participant develops clinical decompensation, no further participants will undergo treatment withdrawal until the formal review by investigators and the DSMB
2. Resumption of treatment withdrawal may occur if the DSMB and investigators determine the safety measures are adequate AND that the benefits of continued study of treatment withdrawal outweighs the risks


DCC will send weekly email reminders to PIs and Coordinators listing participants approaching Week 180 and Week 192 Visits
Week 180 Visit
PI/Participant discussion re: drug discontinuation
PI starts Discontinuation of Study Drug form
Week 192 Visit
PI completes Discontinuation of Study Drug form and site enters all data from visit within 24 hours of the visit
The DCC identifies deviations from discontinuation protocol or discrepancies in reported lab values
Inconsistencies identified or protocol deviation
No inconsistencies identified and no protocol deviation
DCC follows-up with PI
Participant should not discontinue study drug
Participant should discontinue study drug
If protocol violation (e.g. treatment discontinued for participant not eligible to discontinue), PI/site submits Off-Protocol form
If inconsistency, site corrects data
Follow per protocol
PI assessment at every visit to determine if criteria to restart therapy triggered
DCC monitors based on data received
DCC sends Off-Protocol form to monitoring group
DCC provides report to monitors
If a criterion to restart treatment is triggered, tests repeated per protocol
A monitor may follow-up with PI for explanation and report back to monitoring group
Stopping Rule
When data of 2nd clinical decompensation are entered, DCC immediately notifies all PIs, monitors, and DSMB. No further participants will discontinue drug until formal DSMB and investigator review
PI makes decision whether to restart treatment
Protocol criteria to restart are met
Protocol criteria to restart are not met
Follow reinitiation process (p.2)
PI decides not to restart treatment
PI decides to restart treatment
PI/site to enter a Reinitiation of Study Drug and an Off-Protocol form
KEY:
PI/Site
DCC
Monitoring group
Special attention
Off-Protocol form
PI decision point


Reinitiation Process
PI enters Reinitiation of Study Drug form as soon as determination to restart/not restart is made
The DCC identifies deviations from reinitiation protocol or discrepancies in reported lab values
Inconsistencies identified
DCC follows-up with PI
Site corrects data
No inconsistencies identified
DCC sends form to monitors
At least 2 monitors must respond whether protocol criteria to restart treatment are met
Protocol criteria not met
Protocol criteria met
Monitor discusses case with PI and reports back to monitoring group
DCC sends monitoring feedback to PI
If treatment restarted for participant not eligible to restart or treatment not restarted for participant eligible to restart, PI submits Off-Protocol form
Within 72 hours
KEY:
PI/Site
DCC
Monitoring group
Special attention
Off-Protocol form
PI decision point

Template for Discussion with Participant Regarding Antiviral Therapy Discontinuation

Date:
Participant ID:
Person Conducting Review of Consent:
Other Persons Present During Discussion:

Documentation of Discussion:
The consent for the protocol entitled "Combination Therapy of Peginterferon Alfa-2a and Tenofovir versus Tenofovir Monotherapy in HBeAg-positive and HBeAg-negative Chronic Hepatitis B", IRB Approval # XXXX was re-reviewed with the participant today. Specifically, I reviewed:

- The rationale for antiviral discontinuation and the potential benefits and risks.
- The need to assess the participant for eligibility for withdrawal of antiviral therapy at the week 192 visit.
- Plans to discontinue treatment with tenofovir at the week 192 visit if eligibility criteria are met. Remind the participant to continue to take study medication up to and including the day of the week 192 visit.
- Plans for close monitoring of laboratory results after treatment discontinuation with testing done every 4 weeks for the first 6 months, and then every 3 months thereafter for a full year.
- That elevations of HBV DNA and ALT after treatment discontinuation may occur and retreatment may be necessary if the elevations are high enough or persistent.
- If retreatment is needed, that tenofovir will be provided for up to one year (to end of the study) and continuation of treatment thereafter is the responsibility of the participant's insurance.

Confirmation of Continued Participation and Consent to Antiviral Discontinuation and Follow-up Plans:

I have confirmed the participant's understanding of the antiviral discontinuation and follow-up plans and provided him/her with the "Information Sheet on Antiviral Withdrawal".

I have confirmed that the participant wishes to continue participation in the study and agree to discontinue antiviral and follow-up plans if he/she meets eligibility criteria.

Confirmation of Lack of Participation in Antiviral Discontinuation:

I have confirmed the participant's understanding of the antiviral discontinuation and follow-up plans and provided him/her with the "Information Sheet on Antiviral Withdrawal".

I have confirmed that the participant does not wish to participate in antiviral discontinuation if he/she meets eligibility criteria.

I have confirmed that the participant will continue to be followed according to the same schedule as participants who agree to discontinue treatment at week 192.

I have informed the participant that study medication (tenofovir) will not be provided beyond week 192.

I have developed a plan for insuring antiviral therapy is prescribed such that the participants will not have any interruption of therapy.

Investigator signature _____ Date _____

Participant Information Sheet

Thank you for your participation in the HBRN's "Combination Therapy of Peginterferon Alfa-2a and Tenofovir versus Tenofovir Monotherapy in HBeAg-positive and HBeAg-negative Chronic Hepatitis B" study!

You are approaching the final phase of the study. This part of the study evaluates whether the treatment you have received for the past 4 years has resulted in an ability of your own immune system to keep the virus suppressed or not. We will also determine if stopping treatment can produce higher rates of HBsAg loss (the best marker that your hepatitis B infection is controlled).

At your next visit (Week 192), you will be assessed to determine if treatment can be discontinued. If you meet the criteria for stopping treatment, your last dose of tenofovir will be on the date of the Week 192 visit. You should bring your study medication to that visit.

After the treatment is stopped, your study doctors will be monitoring you closely. You will be asked to return for study visits every 4 weeks for the first 6 months, then every 12 weeks until the end of the study. Post-treatment weeks 16 and 20 visits (weeks 208 and 212) may be replaced by phone visit plus local labs. You will be followed for a total of 48 weeks after stopping the study medication.

When the study medication is stopped, it is possible that your level of HBV DNA (viral load) and liver tests (ALT) may become elevated. This may be transient (for a short time only) or more persistent. If the levels are high or if they remain elevated for many months, it may be necessary to restart the tenofovir. Your study doctor will be reviewing the results of the lab tests with you and informing you if tenofovir needs to be restarted. It is important that you obtain the blood tests as requested by your study doctor to allow close monitoring of your condition. In rare cases, the levels can be very high and associated with jaundice (yellow of your eyes) or signs of liver failure. If such cases occur, tenofovir will be restarted as soon as possible.

If you need to restart tenofovir, the drug will be provided by the study only until the end of the study (maximum of 48 weeks from Week 192 visit). After the study is complete, you will need to obtain a prescription for tenofovir (or an alternative medication) through your insurance. Your study doctor will advise you about how to do this.

Participant signature _____ Date _____

Tests **required** at Week 180 visit:

HBeAg*^
Anti-HBe
HBsAg
Platelet count^
ALT
AST
Total bilirubin
Direct bilirubin^
Albumin^
Calcium
BUN
Creatinine
Creatinine clearance (calculated)
Phosphate (PO_4)
INR^
HBV DNA (central lab)^#

* HBeAg positive at baseline – HBeAg test is required at Week 144

^ Results needed to determine eligibility to discontinue study drug at Week 192 visit

HBV DNA central lab results from week 156 through week 180

Discontinuation of Study Drug at Week 192

Patient ID __ __ - __ __ __ __ - __ __ __

Instruction: *Begin to complete this form at the Week 180 visit to document that the investigator reviewed information with the participant and begin determination of whether or not the participant meets the criteria to discontinue study medication at the Week 192 visit.*

The form should be entered in the HBRN database within 24 hours following the Week 192 visit.

SECTION I: PI REVIEW OF STUDY DRUG DISCONTINUATION INFORMATION AT WEEK 180 VISIT

Indicate whether or not the study investigator performed the following:	Yes	No
a. Reviewed rationale for antiviral withdrawal with participant	☐	☐
b. Reviewed criteria for treatment discontinuation with participant	☐	☐
c. Reviewed potential benefits and risks of treatment discontinuation with participant	☐	☐
d. Reviewed criteria for resuming antiviral treatment with participant	☐	☐
e. Reviewed post treatment follow-up schedule with participant	☐	☐
f. Participant given fact sheet reviewed by study investigator	☐	☐
g. Participant signed fact sheet placed in study chart	☐	☐
h. Participant reminded that last dose of tenofovir will be on day of week 192 visit, and to bring all remaining study drug to that visit	☐	☐
i. Investigator documented discussion with participant in participant record Date of discussion *(mm/dd/yy):* ___/___/___	☐	☐

SECTION II: CRITERIA FOR DISCONTINUING STUDY DRUG AT WEEK 192 VISIT (Use lab results from Week 180 visit or most recent prior to Week 192 visit. Do not use lab results from the Week 192 visit.)

Indicate whether or not the participant meets each criterion:	Yes	No
a. No cirrhosis on baseline biopsy; Ishak score (central read): ____ (1-4 = no cirrhosis 5-6 = cirrhosis)	☐	☐
b. HBV DNA <1000 IU/mL for the previous 24 weeks (week 156 through 180) result: _____ date: ___/___/___ result: _____ date: ___/___/___ result: _____ date: ___/___/___	☐	☐
c. Albumin ≥ 3.8 g/dL result: _____ date: ___/___/___	☐	☐
d. INR ≤ 1.3 result: _____ date: ___/___/___	☐	☐
e. Direct bilirubin ≤ 0.5 mg/dL result: _____ date: ___/___/___	☐	☐
f. Platelet count ≥ 120,000/mm^3 result: _____ $x10^3$ date: ___/___/___	☐	☐
g. No evidence of clinical decompensation (ascites, hepatic hydrothorax, variceal bleeding, portal hypertensive bleeding, hepatic encephalopathy, CTP score ≥ 7)	☐	☐
h. No clinical evidence of portal hypertension	☐	☐
i. No radiologic evidence of portal hypertension date of imaging: ___/___/___ (or imaging not clinically indicated, not performed)	☐	☐

j. HBeAg-negative at baseline visit and confirmed at week 180, or HBeAg-positive at baseline visit with HBeAg loss at or before week 144 and confirmed at week 180. In either situation, there can be no HBeAg positive result at or after week 144. Baseline result: ☐ Pos ☐ Neg ☐ Equiv date: ___/___/___ Week 144 result: ☐ Pos ☐ Neg ☐ Equiv date: ___/___/___ Week 180 result: ☐ Pos ☐ Neg ☐ Equiv date: ___/___/___	☐	☐
k. HBsAg-negative (regardless of anti-HBe status), or if HBsAg-positive, HBeAg-negative and anti-HBe-positive at week 180 HBsAg result: ☐ Pos ☐ Neg ☐ Equiv date: ___/___/___ Anti-HBe result: ☐ Pos ☐ Neg ☐ Equiv date: ___/___/___	☐	☐

SECTION III: DETERMINATION OF STUDY DRUG DISCONTINUATION

1. Is participant eligible per protocol to discontinue study drug at week 192: ☐ Yes ☐ No
   a. Date eligibility to discontinue determined *(mm/dd/yy)*: ___ / ___ / ___
2. Was study drug discontinued at Week 192: ☐ Yes ☐ No
   a. If No, reason
      - ☐ Participant not eligible per one or more of the protocol criteria (as listed in Section II)
      - ☐ Participant preference
      - ☐ Study investigator preference
      - ☐ Other, specify _____

Investigator signature: _____

Data collector initials: __ __ __
Date data collection completed *(mm/dd/yy)*: ___ / ___ / ___

Reinitiation of HBV Treatment in Post-treatment Follow-up Period

Patient ID __ __ - __ __ __ __ - __ __ __

Instruction: *Complete this form when the information needed to determine whether or not a participant who discontinued study drug (at the Week 192 visit) will be restarted on any HBV therapy during the post-treatment follow-up period.*

SECTION I: CRITERIA FOR RESTARTING HBV TREATMENT

Indicate whether or not the participant meets each criterion:	Yes	No
a. Total bilirubin ≥ 3.0 mg/dL, regardless of HBV DNA or ALT level Initial result _____ mg/dL Date of sample (*mm/dd/yy*) ___/___/___	☐	☐
b. Direct bilirubin ≥ 1.0 mg/dL, regardless of HBV DNA or ALT level Initial result _____ mg/dL Date of sample (*mm/dd/yy*) ___/___/___	☐	☐
c. INR ≥ 1.3, regardless of HBV DNA or ALT level Initial result _____ Date of sample (*mm/dd/yy*) ___/___/___	☐	☐
d. Evidence of clinical decompensation (ascites, hepatic hydrothorax, variceal bleeding, portal hypertensive bleeding, hepatic encephalopathy, CTP score ≥ 7)	☐	☐
e. HBV DNA and ALT values meet one of the below criteria (check the specific criterion below) HBV DNA ≥ 10,000 IU/mL Initial result (UWash central lab) _____ IU/mL Date (*mm/dd/yy*) ___/___/___ Initial ALT _____ U/L Date (*mm/dd/yy*) ___/___/___ Repeat ALT _____ U/L Date (*mm/dd/yy*) ___/___/___ Repeat ALT _____ U/L Date (*mm/dd/yy*) ___/___/___ ☐ HBV DNA ≥10,000 IU/mL and **ALT >1000 U/L (male or female)** (i.e. only one ALT values >1000 U/L is needed to qualify) **Or** ☐ HBV DNA ≥10,000 IU/mL and **ALT ≥300 U/L for males, ≥200 U/L for females**. A total of one HBV DNA ≥10,000 IU/mL and any 3 ALT values ≥300 (male) or ≥200 U/L (female) over a 4-week (or longer) time frame are needed to qualify. Treatment will be resumed if the third ALT remains ≥300 U/L (male) or ≥200 U/L (female). **or** ☐ HBV DNA ≥10,000 IU/mL and **ALT ≥150 U/L for males or ≥100 U/L for females**. A total of one HBV DNA ≥10,000 IU/mL and any three ALT values ≥150 U/L (male) or ≥100 U/L (female) over the 12 week (or longer) time period are needed to qualify. Treatment will be resumed if the third ALT remains ≥150 U/L (male) or ≥100 U/L (female).	☐	☐
f. At week 192, HBsAg positive and HBeAg positive OR HBsAg positive, HBeAg negative, and anti-HBe negative	☐	☐
g. Other, specify _____	☐	☐

SECTION II: DETERMINATION TO REINITIATE HBV TREATMENT

1. Is participant eligible to restart treatment: ☐ Yes ☐ No

   a. Date eligibility to restart determined *(mm/dd/yy)*: ___ / ___ / ___

2. Was treatment restarted: ☐ Yes ☐ No

   If restarted: Date restarted (*mm/dd/yy*): ___ / ___ / ___

   Drug restarted: ☐ Tenofovir ☐ Other, specify _____

   If not restarted, reason

   ☐ Participant not eligible per criteria (listed in Section 1)
   ☐ Participant preference
   ☐ Study investigator preference
   ☐ Other, specify _____

Investigator signature: _____

Data collector initials: __ __ __

Date data collection completed *(mm/dd/yy)*: ___ / ___ / ___

Implementation of Stopping Rule

Monitoring treatment reinitiation and clinical decompensation

- A Treatment Reinitiation record is to be submitted to the database within 24 hours of the decision to restart treatment (page 2 of flowsheet-Reinitiation Process). The data management system (DMS) will send email notifications to DCC data managers and project coordinators.
- The DCC data managers and project coordinators will review the information submitted and get back to the site coordinator for additional information if necessary.
- The DCC project coordinators will send the form to the monitors (Jay Hoofnagle, Averell Sherker, Obaid Shaikh, and Rob Squires), at least 2 of whom must respond within 72 hours to the DCC whether protocol criteria were met. PI is notified of monitors' assessment whether protocol criteria to restart treatment were met.
    - If monitors indicate that the protocol criteria were <u>not</u> met, the monitor will discuss the case with the PI and report back to the monitoring group.
    - If it was determined that treatment was restarted for a participant who was not eligible to restart or treatment was not restarted for a participant eligible to restart, the PI must submit an Off-Protocol form (page 2 of flowsheet-Reinitiation Process).

Notification and suspension of treatment discontinuation

- The DMS will send email notifications to DCC personnel (data managers and project coordinators) when clinical decompensation is reported in a participant following treatment withdrawal. The DCC will confirm the event with the site and then DCC project coordinators will forward the notification to all site PIs.
- Within 24 hours of the email notification of a second participant with clinical decompensation, a DCC project coordinator will notify all site PIs, site coordinators, the HBRN Safety Monitors, NIDDK personnel, and Executive Secretary of the event. PIs will be instructed to suspend treatment discontinuations immediately until further notice.
    - PIs from each site will be required to acknowledge receipt of email and confirm that they have stopped treatment discontinuations.
- The reinitiation forms and supporting information from the two decompensation cases will be sent to the Steering Committee, Safety Monitors, NIDDK personnel, and the Executive Secretary of the DSMB, within 48 hours of the email notification of the second participant with clinical decompensation.

Formal review process

- The DCC will convene the Steering Committee for a formal review via teleconference within 14 days of the second decompensation notification.
- The Steering Committee decision will be forwarded to the Executive Secretary of the DSMB in advance of the DSMB formal review.
- The NIDDK will request a formal review by the DSMB within 14 days after the Steering Committee formal review. The Executive Committee and HBRN safety monitors will attend as appropriate.

Next Steps

- The DSMB recommendation will be forwarded to the DCC project coordinators by NIDDK within 2 days of the formal review. If the DSMB requires additional information to render a decision, the site PI must provide it to the DCC project coordinators within 7 days of the request, who will then forward it to the Executive Secretary of the DSMB.
- The DCC project coordinators will communicate the DSMB recommendations (e.g. permanently discontinue treatment discontinuations, resume treatment discontinuations, etc) to the site PIs and coordinators through a special email alert.
    - PIs from each site will be required to acknowledge receipt of email and confirm that they will comply with recommendation.