HALT-C Adverse Event Reporting

I. Introduction

In clinical studies, subjects may experience adverse events, that is, unwanted effects on the body. Identifying, classifying, recording and reporting adverse events ensures that study subjects are protected and that clinical centers, the Data Coordinating Center (DCC), and sponsors are acting responsibly within federal regulations.

II. Definition

A. An *adverse event* (AE) is defined as any adverse change from the patient's baseline (pre-screening) condition (including intercurrent illness or symptoms), which occurs during the course of the trial (from the time the screening consent is signed), whether considered related to treatment or not. In the HALT-C Trial, adverse events will be documented from the time of the first Screening Visit through Study Month 54.

B. A *serious adverse event* (SAE) is defined as any untoward medical occurrence that:

- Results in death.

C. Also, an *SAE* is defined as any untoward medical occurrence that is <u>not</u> a clinical outcome as defined by the HALT-C protocol and meets one or more of the following conditions:

- Is life-threatening (there is a risk of death at any time during the event);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly or birth defect; and/or
- Is an important medical event (based on appropriate medical judgment) that may jeopardize the patient and may require medical or surgical intervention to prevent one of the conditions listed above.

- In the HALT-C Trial, the first instance of a clinical outcome (except death) is not considered a serious adverse event. Instead, Form #63: Clinical Outcome should be completed.

- 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 analyses and no additional HALT-C forms need to be completed or data entered.

III. Procedures

A. Reporting

1. <u>Notification to the DCC</u>

a. *Adverse events* (AEs)

i. AEs should be reported in a timely fashion by entering **Form #60: Adverse Event Report**, into the Data Management System (DMS). AEs should be reported whenever the clinician is made aware of an AE. This reporting may occur during or between study visits.

ii. All ongoing AEs (those with ongoing status) should be updated at subsequent follow up visits until they are resolved. Any change in AE information should be added to the Form #60 and entered into the DMS using the event number already assigned to that AE.

iii. AEs should be reported from the time the patient signs the screening consent form through Month 54 (6 months post trial follow up) for patients in the Randomized Phase and through Week 72 for patients in the Responder Phase. Patients who terminate their Trial participation prematurely must have AEs reported for six months post-treatment, if possible.

iv. No AEs will be collected at Study Months 60 and 72.

2. Notification to the DCC and Hoffmann-La Roche

b. *Serious adverse events* (SAEs)

i. All SAEs should be reported to the DCC by telephone within 24 hours of learning of the event to:

Margaret Bell
New England Research Institutes, Inc.
9 Galen Street
Watertown, MA 02472
Phone: (617) 923-7747, X 522
Fax: (617) 926-0144
Email: MBell@NERI.org

ii. Complete **Form #60: Adverse Event Report.** Data entry of Form #60 allows the DMS to assign an event number to the adverse event and allows the event to be added to the patient's adverse event log. If the severity of an adverse event (B5d on Form #60) is serious (3), then a Serious Adverse Event or a Clinical Outcome will be expected.

iii. Complete **Form #61: Serious Adverse Event Report** using the same event number as on the Form #60. Enter event number assigned by the DMS when Form #60 Adverse Event Report is data entered for this serious adverse event.

iv. Fax Form #61 to the DCC within 24-48 hours of learning of the event. Source documents may be requested and sent at a later date.

v. For any patient who is presently or in the past 6 months has been on study medication, fax Form #61 to Hoffmann-La Roche within 24-48 hours of learning of the event to:

Dr. Cliff Joseph
Phone: (973) 562-3613
Fax: (973) 562-3602

vi. If further information becomes available, one or more additional paper Form #61s will need to be completed in the following manner:

- Complete Section A with any updates including A6 (date of new information).
- Leave blank anything that is not new or changed information. For example, if everything is exactly the same as the first Form #61 except that the event is now resolved, Section A will be completed, questions E1 and E4 will be completed,

Section I2 will be updated, and Section M will be completed. Leave blank all other information that has not changed since last filling out Form #61 for the same event and same patient.
- Any follow-up form should also be faxed to the DCC and Hoffmann-La Roche (if applicable) with telephone notification.

vii. SAEs should be reported from the time the patient signs the screening consent form through Month 54 (6 months post trial follow up) for patients in the Randomized Phase and through Week 72 for patients in the Responder Phase. Patients who terminate their Trial participation prematurely must have SAEs reported for six months post-treatment, if possible.

viii. No SAEs will be collected at Study Months 60 and 72.

ix. No SAEs will be collected on clinical outcomes. If an event is sent to the clinical outcome review board and it is determined that the event did not meet the clinical outcome criteria, it should then be reported as an SAE, if appropriate.

3. Notification to FDA, NIDDK, DSMB, Steering Committee, Clinical Center IRBs, and Principal Investigators: In accordance with Federal Guidelines, the DCC will notify the appropriate agencies of serious adverse events.

a. *Expedited reporting*

i. Any adverse events deemed to be serious, unexpected, and associated with the use of the trial medication will be reported immediately (as defined below) to:
- Food and Drug Administration (FDA),
- National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK),
- Data and Safety Monitoring Board (DSMB),
- Hoffmann-La Roche,
- All participating investigators.

ii. Those events that are considered life threatening or result in death will be reported as soon as possible and within 7 calendar days of notification by the site. Initial reporting may be done by telephone or fax. Written confirmation of the event and any additional information will be reported within 8 calendar days of the initial report. If the event is not life threatening or fatal, a written report will be sent as soon as possible and within (15) calendar days. FDA Form #3500A will be used to report these events. A copy of the completed form will be kept at the DCC, along with the original site data forms and source documents.

iii. Serious events are those which are life threatening (there is an immediate risk of death at the time of the event) OR which require hospitalization or the prolongation of an existing hospitalization OR which result in persistent or significant disability or incapacity; OR which result in death.

iv. Unexpected events are those that are inconsistent with the severity and/or specificity defined in the Investigator's Brochure.

v. Events associated with the use of the trial medication are defined in section IV.B.4.

b. *Non-expedited reporting*

i. Annual Reports must be submitted to the FDA by the DCC within 60 days of the

anniversary of IND. The summary of safety information reported must include:

- Summary of all IND safety reports (7 and 15 day reports).
- Non-serious events.
- Serious but not study drug related events.
- Serious but expected events.
- SAEs by body system,
- Deaths.
- Any patient discontinuations due to AEs.

c. *Additional reporting to the Clinical Center IRB*

i. The DSMB is responsible for sending a summary report to each clinical center that will forward the information to their individual IRB following each meeting.

ii. The clinical center Principal Investigator is also responsible for notifying their own IRB of possible trial related adverse events occurring at their particular site, according to institutional procedure.

B. Forms to complete

1. Required forms. These forms must be completed when an adverse event is reported:

- Form #60, Adverse Event Report: Complete for all adverse events.
- Form #61, Serious Adverse Event Report: Complete and update when applicable, if the event is serious.

2. As needed forms. The following forms may need to be completed when an AE occurs:

- Form #19, Early Termination of Peginterferon-alfa 2aTreatment: Complete if the AE resulted in the permanent cessation of Peginterferon-alfa 2a.
- Form #25, Early Termination from Trial: Complete if the AE resulted in early termination from the Trial.
- Form #28, Peginterferon-alfa 2a Dose Adjustment: Complete if dose adjustment or cessation of Peginterferon-alfa 2a is required due to an AE.
- Form #29, Ribavirin Dose Adjustment: Complete if dose adjustment or cessation of ribavirin is required due to an AE.
- Form #63, Clinical Outcomes: Complete any time a clinical outcome occurs. **ALL** clinical outcomes, with the exception of two consecutive CTP scores of or equal to 7, are considered adverse events.
- Form #64, Death: Complete anytime a death occurs, no matter what the cause. **ALL** deaths are considered SAEs.

C. Source documentation

1. Definition: A source document is a part of the patient's medical record and serves to validate data collected on data entry forms.

2. Appropriate source documentation: For each AE, the pertinent portions of the patient's medical records documenting the event should be selected, for example lab reports, ER documents, discharge summaries, etc.

D. Adverse Event Terminology: These terms should be used to define all adverse events.

1. AE Severity: AEs will be judged on the severity of the incident as follows:

a. *Mild:* Defined as causing discomfort, but with no disruption of normal daily activity.

b. *Moderate:* Defined as causing discomfort sufficient to reduce or affect normal daily activity.

c. *Serious:* Defined as one of the following:
- A situation which is life threatening (immediate risk of death at the time of the event).
- A situation that requires hospitalization or prolongation of existing hospitalization.
- A situation that results in persistent or significant disability or incapacity.
- A situation that results in death.

2. Relationship of the AE to Trial Medication: AEs will be judged based on their relationship to either or both trial medications as follows (also see Table 1):

a. *Unrelated:* This category applies to AEs which, after careful medical consideration at the time of evaluation, are judged to be clearly and incontrovertibly due to extraneous causes (disease, environment, etc.) and do not meet the criteria for drug relationship listed under remote, possible, or probable.

b. *Remote:* This category is applicable to an AEs which meets the following criteria (must have first two):
- It does not follow a reasonable temporal sequence from administration of trial medication(s).
- It could readily been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.
- It does not follow a known pattern on response to the suspected trial medication(s).
- It does not reappear or worsen when the trial medication(s) is (are) re-administered.

c. *Possible:* This category applies to those AEs in which the connection with administration of the trial medication(s) appears unlikely, but cannot be ruled out with certainty. The following criteria are defined (must have first two):
- It follows a reasonable temporal sequence from administration of trial medication(s).
- It may have been produced by the patient's clinical state, environmental or toxic factors or other modes of therapy administered to the patient.
- It follows a known pattern of response to the suspected drug(s).

d. *Probable:* This category applies to those AEs that are considered, with a high degree of certainty, to be related to trial medication(s). The following should occur (must have first three):
- It follows a reasonable temporal sequence from administration of the trial medication(s).
- It could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic effects, or other modes of therapy administered to the patient.
- It disappears or decreases on cessation or reduction in dose of trial medication(s). There are important exceptions when an AE does not disappear upon discontinuation of the trial medication(s), yet drug relatedness clearly exists; for example, bone marrow depression or tardive dyskinesias.

- It follows a known pattern of response to the suspected trial medication(s).
- It appears on rechallenge.

3. Pattern of Events:

   a. *Single event:* Defined as an event that occurs just once and has ended by the time it is reported.

   b. *Continuous:* Defined as an event that began just once and is still ongoing at the time of reporting.

   c. *Intermittent:* Defined as an event that has gone through at least one cycle of starting, stopping, and starting again.

4. AE Status:

   a. *Resolved, no residual effect:* After the AE ends, the patient returns to pre-AE status.

   b. *Resolved with sequelae:* After the AE ends, the patient does not return to pre-AE status.

   c. *Continuing:* The AE is still ongoing at the time of the report.

   d. *Disability:* An AE that has caused a substantial disruption of the person's ability to conduct normal life functions.

   e. *Death*.

5. Actions to be taken: Any of the following actions can be taken during the course of an adverse experience:
   - None
   - Additional therapy (such as surgery, or physical or occupational therapy, acupuncture, etc.)
   - Additional lab tests
   - Additional medication
   - Peginterferon-alfa 2a reduced
   - Peginterferon-alfa 2a temporarily discontinued
   - Peginterferon-alfa 2a permanently discontinued
   - Ribavirin reduced
   - Ribavirin temporarily discontinued
   - Ribavirin permanently discontinued
   - Hospitalization needed
   - Hospitalization prolonged

IV. Death Reporting Procedures

A. How to report a death

1. All patient deaths must be reported via telephone, to the DCC, within 24 hours of site notification to:

Margaret Bell
New England Research Institutes, Inc.
9 Galen Street
Watertown, MA 02472
Phone: (617) 923-7747, X 522
Fax: (617) 926-0144
Email: MBell@NERI.org

2. All deaths should be reported from the time the patient signs the trial consent through Month 54 (6 month post trial follow-up) for randomized patients or through Study Month 60 and Study Month 72 (for those patients participating in the Extended Follow-up Phase) and through Week 72 for patients in the responder phase. Patients who terminate their Trial participation prematurely must have adverse events reported for six months post-treatment, if possible.

B. Forms to complete:

- Form #60, Adverse Event Report.
- Form #61, Serious Adverse Event Report should be completed and faxed within 24 hours of notification of death.
- Form #63, Clinical Outcomes should also be completed and faxed to the DCC for review as above.
- Form #64, Death Report should be completed and faxed to the DCC within 24 hours of notification of the death. When more information is available, the form should be updated. Refer to QxQ for Form #64 for details.

C. Source Documentation:

1. Further documentation of the death should be faxed or mailed to the DCC as soon as they become available. Every attempt should be made to obtain information from outside sources, including other hospitals, clinics, hospices, nursing homes, etc. Source documents can include any of the following:
   - Death certificate
   - Autopsy report
   - Notation in any medical/research record (hospice, nursing home, hospital, etc.) pronouncing date and time of death and signed by appropriate medical practitioner (for example, “Patient resuscitation stopped and patient pronounced dead at 12:37 PM on 3/30/00, signed John Smith, MD”)
   - Notation in the medical/research record reporting details of death (for example, “Patient’s wife notified staff of patient’s death in a car accident on 3/30/00”)

2. Copies of the source documents for deaths should be kept with the data entry forms in patient study notebook. Identifying information, such as patient name and medical record should be blacked out and replaced with the patient ID number (labels provided by the DCC may be used).

V. Dose Adjustments:

This section will detail the adjustments that can and should be made to the doses of trial medications, Peginterferon-alfa 2a and Ribavirin. Every dose adjustment is based on the Principal Investigator's clinical judgment of the relevant situation. Information on dose modification and cessation can also be found in sections L and M of the HALT-C protocol.

A. Peginterferon-alfa 2a

1. Dosages of Peginterferon alfa-2a

a. *Lead in Phase:*
- Patients will begin the Lead in Phase of the HALT-C Trial with a Peginterferon-alfa 2a dose of 180 μg sc weekly.
- Those patients with a low ANC or platelet count will begin the Lead-in Phase with a Peginterferon-alfa 2a dose of 90 μg sc weekly. See Table 4, page 14 of this section for further details.

b. *Randomized Phase:*
- Non-responders who are randomized to receive Peginterferon-alfa 2a will have their dose reduced to 90 μg sc weekly.

c. *Responder Phase:*
- Responders will continue on the initial dose of 180 μg sc weekly for an additional 24 weeks, stopping drug at Week 48.

2. Dose reductions of Peginterferon alfa-2a

a. Certain symptoms, laboratory values, or adverse events may lead to a protocol mandated reduction in the dose of Peginterferon-alfa 2a. Every attempt will be made to keep those patients randomized to treatment with Peginterferon-alfa 2a on therapy by dose reduction.

b. Tables 2 - 5 of this section provide guidelines for dose reduction.
- Table 2: Gives general dose reduction guidelines for effects including, but not limited to disabling symptoms (such as fatigue, dizziness, or depression); rashes; changes in vital signs; and lab values not specified below.
- Table 3: Provides required dose adjustments for decreases in neutrophil and platelet counts through week 24.
- Table 4: Details required dose adjustments and safety regulations for patients entering the Lead-in Phase of the trial with low ANC or low platelet counts.
- Table 5: Details required adjustments for increases in serum ALT through week 24.

c. Factors that will lead to a reduction in the dose of peginterferon alfa-2a include:
- Disabling symptoms, which, in the opinion of the investigator, are related to peginterferon alfa-2a treatment and prevent the patient from performing his/her occupation or daily tasks.
- A rash consistent with allergic reaction or vasculitis.
- Reductions in the platelet count according to the guidelines in Appendix D4.
- A reduction in neutrophil count according to the guidelines in Appendix D4.
- Any adverse reaction, which, in the opinion of the investigator, places the patient at increased risk.

d. There are 3 prescribed levels for dose reduction. The dose of peginterferon alfa-2a may be reduced as follows:
   - 135 μg
   - 90 μg
   - 45 μg

e. During the randomized phase 90μg may be reduced to 45 μg for cytopenias or other side effects. Peginterferon alfa-2a can be increased to 90μg at the investigator's discretion.

3. Increasing the dose following dose reduction of peginterferon alfa-2a. Once a patient's dose has been decreased, the investigator may attempt to increase the dose back to or toward the previous stable level only if the following conditions are satisfied:

   a. The event or circumstance responsible for the dosage adjustment has resolved or improved.

   b. The patient has been at the lower dose for ≤4 consecutive doses; ≤6 total doses have been administered to the patient at the lower level during the entirety of the treatment period.

   c. As a guideline, patients who have received more than 4 consecutive or 6 total doses of peginterferon alfa-2a at the lower dose level should not have their dosage regimen readjusted upward. If 4 or more consecutive doses of peginterferon alfa-2a are held or otherwise not administered (i.e., the patient has not received test medication for more than 28 days), the patient should be considered intolerant of the test medication or non-compliant, whichever is more appropriate to the clinical situation. In such cases, the investigator should consider discontinuation of study medication.

   d. Every attempt will be made to keep those patients randomized to treatment with peginterferon alfa-2a on therapy by dose reduction.

B. Ribavirin

1. Dosages of Ribavirin

   a. *Lead-in Phase*
      - Patients will begin the Lead in Phase of the HALT-C Trial with a Ribavirin dose of 1000 mg or 1200 mg (depending on body weight, above or below 75 kg) po per day.
      - For those patients who have documented intolerance to ribavirin, no ribavirin will be given during the Lead-in Phase, per the Principal Investigator's clinical judgment.

   b. *Randomized Phase*
      - Non-responders will stop taking Ribavirin at randomization.

   c. *Responder Phase*
      - Patients in the responder phase will continue on the initial dose of 1000 mg or1200 mg for an additional 24 weeks.

2. Dose reductions of Ribavirin. Certain symptoms, laboratory values, or adverse events may lead to a protocol mandated reduction in the dose of Ribavirin. Patients may stay on a permanently reduced dose of Ribavirin or come off Ribavirin completely and remain in the trial. The following factors will lead to mandatory reduction in the dose of Ribavirin:

a. For patients *without* significant cardiovascular disease who experience a fall in hemoglobin to <10 g/dL and >8.5 g/dL during any 4 weeks of treatment: Reduce the Ribavirin dose to 600 mg per day (200 mg in the morning and 400 mg in the evening). Further reductions may be considered at the investigator's discretion.

b. For patients *with* stable cardiovascular disease who experience a fall in hemoglobin by >2 g/dL during any 4 weeks of treatment: Reduce the Ribavirin dose to 600 mg per day (200 mg in the morning and 400 mg in the evening). Further reductions may be considered.

c. All patients who have more than a 3 g/dL decrease from baseline in their hemoglobin concentration should have an appropriate work-up for anemia, including reticulocyte count, search for sources of bleeding, etc., especially if a further drop occurs following some weeks of apparently stable hemoglobin levels on ribavirin.

3. Cessation of Ribavirin therapy. Ribavirin should be discontinued under the following circumstances:
   - If a patient without significant cardiovascular disease experiences a fall in hemoglobin confirmed to be less than 8.5 g/dL.
   - If a patient with stable cardiovascular disease maintains a hemoglobin value <12 g/dL despite 4 weeks on a reduced dose.

4. Increasing the dose of Ribavirin following a dose reduction. In the event of Ribavirin being discontinued, it can be reintroduced at a daily dose of 600 mg and increased thereafter at the investigator's discretion. It is not considered necessary to tailor the reduced dosing according to the 75 kg cut-off level.

C. Pregnancy: There are special considerations for patients or partners of patients who become pregnant during the HALT-C Trial.

1. Lead in Phase and Responder Phases

a. If a patient becomes pregnant during the Lead-in or Responder Phases, all treatment will be stopped and she would not be eligible for the Randomized phase of the Trial.

b. If the partner of a male patient becomes pregnant during the Lead-in Phase or Responder Phase, Ribavirin will be stopped, but not Peginterferon alfa-2a. The male patient and his pregnant partner(s) will be advised to use barrier method of contraception for the remainder of the pregnancy after the ribavirin is stopped during the pregnancy, and postpartum as long as the male patient's partner(s) is breast feeding.

2. Randomized Phase

a. If a patient becomes pregnant during the Randomized Phase, treatment will be discontinued for the duration of the pregnancy. Treatment may be resumed three months post-partum if the patient is not breast-feeding.

b. If the partner of a male patient becomes pregnant during the Randomized Phase the male patient and his pregnant partner(s) will be advised to use a barrier method of contraception if the pregnancy occurs within six months of the use of ribavirin.

D. Permanent Discontinuation of Trial Medication

1. Situations which require the permanent discontinuation of study therapy: There are several situations that require the permanent discontinuation of study therapy, outlined below. See

Section H, Trial Medications, of the Manual of Operations for more information on the procedures for permanently discontinuing trial medication.

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

2. By these criteria, onset of ascites, variceal hemorrhage, or hepatic encephalopathy do not require discontinuation of peginterferon alfa-2a but may lead to withholding further therapy if, in the opinion of the investigator, continuation is not in the patient's best interest.

3. Randomized patients who stop receiving peginterferon alfa-2a 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 24 weeks except for follow-up on all unresolved adverse events.

E. Forms to be completed for dose modifications (see QxQs for further details)

- Form #10, Study Visit: Use this form to indicate any missed doses of peginterferon alfa-2a or ribavirin, either patient initiated or initiated by any physician outside the HALT-C Trial.
- Form #28, Peginterferon-alfa 2a Dose Adjustments: Use this form to document adjustments to the dose of Peginterferon-alfa 2a, including increases and decreases, whether mandated by the HALT-C PI or coordinator, and when the dose is permanently terminated.
- Form #29, Ribavirin Dose Adjustments: Use this form to document adjustments to the dose of Ribavirin, including increases and decreases, when mandated by the HALT-C PI or coordinator, and when the dose is permanently terminated.
- Form #19, Early Termination of Peginterferon-alfa 2a Treatment: Complete this form if Peginterferon-alfa 2a treatment is terminated for any reason other than completing the HALT-C Trial.
- Form #60, Adverse Event Report: Complete this form is an adverse event lead to the modification or discontinuation of therapy.
- Form #61, Serious Adverse Event Report: Complete and update this forms if a serious adverse event leads to the modification of therapy.
- Form #63, Clinical Outcome: Complete this form if a clinical outcome led to the modification or discontinuation of therapy.

F. Source documents: Dose adjustments (increases or decreases) or discontinuations should be recorded in the patient's record each time one occurs. Include the date of the dose adjustment, the study week, new and old doses of medication, and the reason for the dose adjustment.

TABLE 1
Relationship of Adverse Event to Trial Medication

	Unrelated	Remote	Possible	Probable
Clearly due to extraneous causes	+	-	-	-
Reasonable temporal association with Trial drug administration	-	-	+	+
May be produced by patient's clinical state	+	+	+	-
Known response pattern to suspected drug	-	-	+	+
Disappears or decreases on stopping or reduction in dose	-	-	-	+
Reappears on rechallenge	-	-	-	+

TABLE 2
General Dose Reduction Guidelines

Number of Dose Reduction Levels (see Section M.1.b.)					
Mild	Moderate Limited	Moderate Persistent	Severe Limited	Severe Persistent	Life-Threatening
0	0	0 – 1	0 - 1	1 – 2	Stop Drug

TABLE 3
Dose Adjustments for Low Absolute Neutrophil and Platelet Counts

Parameter	Downward Dose Adjustment
ANC (cells/mm^3)	
≥1000	None
750 - 999	• Week 1 - 2*: Immediate 1 Level adjustment • Week 3 and greater**: None
500 - 749	• Week 1 - 2: Delay or hold dose until ≥750 then resume dose with 1 Level adjustment • Week 3 and greater: Immediate 1 Level adjustment
250 - 499	• Week 1 - 2: Delay or hold dose until ≥750 then resume dose with 2 Level adjustment • Week 3 and greater: Delay or hold dose until ≥750 then resume dose with 1 Level adjustment
<250	Stop Drug
Platelet Count (cells/mm^3)	
≥50,000	None
35,000 - 49,000	Delay or hold dose until ≥50,000 then resume dose with 1 Level adjustment
25,000 - 34,000	Delay or hold dose until ≥50,000 then resume dose with 2 Level adjustment
<25,000	Stop Drug

*Week 1-2: Signifies the abnormality was noted within the first 2 weeks of the initiation of test drug treatment.
**Week 3 and greater: Signifies the abnormality was noted more than 2 weeks following the initiation of test drug treatment.

TABLE 4
Dose Adjustments for Low Absolute Neutrophil and Platelet Counts for patients who enter the trial with neutrophils between 1,000/mm^3 to 1,500/mm^{3}and Platelet Count from 50,000/mm^3 up to 75,000/mm^3.

Platelet Count (cells/mm^3)	Downward Dose Adjustment
≥40,000	None
20,000 - 40,000	Delay or hold dose for 1 week until ≥40,000 then resume dose with 1 Level adjustment
<20,000	Stop Drug

ANC (cells/mm^3)	Downward Dose Adjustment
≥750	None
250 - 750	Delay or hold dose until ≥750 then resume dose with 1 Level adjustment
<250	Stop Drug

Safety measures for patients with platelet count under 75,000/mm^3 and/or neutrophils under 1,500/mm$^{3:}$

1. The ribavirin should be unchanged but may be lowered at the PI's discretion. Patients will start at a reduced dose of 90 μg of peginterferon alfa-2a once weekly.
2. Patients will be monitored more closely by adding a CBC with differential blood tests at Week 1 and Week 6.
3. Patients will be asked to hold weekly dose of peginterferon alfa-2a until the PI assesses the results of the CBC with differential blood test.

Patients entering Lead-in with a lowered platelet and/or neutrophil count will have ongoing monitoring by the DSMB for the first 8 weeks of treatment.

A separate dose reduction scheme will be followed for these patients as indicated in Table c above.

Dose adjustment upwards is at the discretion of the PI after 8 weeks in the Lead-in.

TABLE 5
Dose Adjustments for Elevated Serum ALT

Baseline Serum [ALT]	On-Treatment Serum [ALT]	Downward Dose Adjustment
≤100	<200	None
	200 – 300	Repeat test in 1 week. If ALT decreased or stable (≤10% increase), continue at present dose and follow every 1-2 weeks to assure stability. If increased by >10%, decrease dose by 1 Level and follow with weekly testing until ALT is stable or decreased.
	301 – 500	Repeat test prior to administering dose. If ALT decreased or stable (≤10% increase), decrease by 1 Level and follow weekly to assure stability. If increased by >10%, hold dose until ALT decreases to <300 then resume test drug at 2 Level decrease and follow every 1-2 weeks until stable. If a further 10% increase occurs, stop test drug.
	>500	Hold test drug until ALT decreased to <300 then resume test drug at 2 Level decrease and follow every 1-2 weeks. If ALT >300, stop test drug.
101 - 200	≤300	None
	301 – 500	Repeat test prior to administering dose. If ALT decreased or stable (≤10% increase), decrease by 1 Level and follow weekly to assure stability. If increased by >10%, hold dose until ALT decreases to <300 then resume test drug at 2 Level decrease and follow every 1-2 weeks until stable. If a further 10% increase occurs, stop test drug.
	>500	Hold test drug until ALT decreased to <300 then resume test drug at 2 Level decrease and follow every 1-2 weeks. If ALT >300, stop test drug.
201 – 300	≤400	None
	401 – 500	Repeat test prior to administering dose. If ALT decreased or stable (≤10% increase), decrease by 1 Level and follow weekly to assure stability. If increased by >10%, hold dose until ALT decreases to <300 then resume test drug at 2 Level decrease and follow every 1-2 weeks until stable. If a further 10% increase occurs, stop test drug.
	>500	Hold test drug until ALT decreased to <300 then resume test drug at 2 Level decrease and follow every 1-2 weeks. If ALT >300, stop test drug.
301 - 500	≤500	None
	>500	Repeat test prior to administering dose. If ALT decreased or stable (≤10% increase), decrease by 1 Level and follow weekly to assure stability. If increased by >10%, hold dose until ALT decreases to less than baseline then resume test drug at 2 Level decrease and follow every 1-2 weeks until stable. If a further 10% increase occurs, stop test drug.
> 500	≤25% Increase	None
	>25% Increase	Repeat test prior to administering dose. If ALT decreased or stable (≤10% increase), decrease by 1 Level and follow weekly to assure stability. If increased by >10%, hold dose until ALT decreases to less than baseline then resume test drug at 2 Level decrease and follow every 1-2 weeks until stable. If a further 10% increase occurs, stop test drug.

Note: This table is based on an upper limit of normal (ULN) serum ALT of 43 U/L for men and 34 U/L for women. The ULN at the local laboratory should be considered when employing this table.

Event Codes List: Common Adverse Events by Symptom/Siagnosis

For use on Forms #60, #61, #63 & #64

These are common symptoms and diagnoses reported for patients with Hepatitis C who are taking interferon and/or ribavirin. If you do not find the code here, please check the ICD-9 code list before contacting the DCC for assistance.

- *Please specify when a symptom is related to a liver biopsy or injection site*.
- PLEASE DO NOT USE 799.9.
- indicates a diagnosis

Symptom	ICD-9 code	Comments
*Arthritis	716.9	
*Asthma	493	
*Bronchitis	490	
*Diabetes	250.0	
*Hypertension	401.9	
*Hyperthyroidism	242.9	
*Hypotension	458.9	
*Hypothyroidism	244.9	
Abdominal pain (general or non-specified location)	789.0	
Abdominal Tenderness	789.6	
Alopecia	704	
Anemia	285.9	
Anorexia (loss of appetite)	783.0	
Anxiety	300.00	
Appetite, decreased or loss of	783.0	
Arm cramp	729.82	
Arrythmias	427.9	
Arthralgia	719.4	
Ascites	789.5	
Back ache, unspecified	724.5	
Blurred vision	368.9	

Symptom	ICD-9 code	Comments
Body aches	780.9	
Bruising at injection site	924.99	
Cellulitis	682	Specify body part
Chest congestion	514	
Chest pain	786.5	
Chills	780.99	
Coma (diabetic)	250.3	
Coma (hepatic)	572.2	
Confusion	298.9	
Congestion, chest	514	
Congestion, nasal	478.1	
Constipation	564.0	
Cough (non-productive)	786.2	
Cramps—limbs	729.82	Specify arm or leg
Decrease or loss of interest in sex	302.71	
Decreased appetite	783.0	
Decreased libido	302.71	
Decreased mental status	300.9	
Decreased platelet count	287.5	
Decreased red blood cell count	790.0	
Decreased white blood cell count	288.8	
Depression	311	
Diaphoresis	780.8	
Diarrhea	787.91	
Discomfort at injection site	782.0	
Disturbance, visual (non-specific)	368.9	
Dizziness	780.4	
Dry skin	701.1	

Symptom	ICD-9 code	Comments
Dyspepsia	536.8	
Dysuria	788.1	
Edema (localized)	782.3	
Emotional lability	300.9	
Epistaxis	784.7	
Erythema at injection site	695.99	
Excessive Sweating	780.8	
Extremity pain	729.5	
Fainting	780.2	
Fatigue	780.79	
Fever	780.6	
Flatulence	787.3	
Forgetfulness	780.9	
Generalized muscle weakness	780.79	
Hair thinning	704	
Headache (migraine)	346.0	
Headache (non-specific)	784.0	
Headache (tension)	307.81	
Heartburn	787.1	
Hepatomegaly	789.1	
High blood pressure (no diagnosis of HTN—non-specific)	796.2	
Hyperbilirubenemia	782.4	
Icterus	782.4	
Impotence	302.72	
Increased AST	790.4	
Indigestion	536.8	
Induration at injection site	782.99	
Injection site, bruising	924.99	

Symptom	ICD-9 code	Comments
Injection site, erythema	695.99	
Injection site, induration	782.99	
Injection site, not specified here	782.99	
Injection site, pain	782.99	
Injection site, redness	695.99	
Injection site, swelling	782.99	
Insomnia	780.52	
Irritability	799.2	
Itching	698.9	
Jaundice	782.4	
Joint aches/pains	719.4	
Leg cramp	729.82	
Lethargy	780.79	
Leukopenia	288.0	
Lightheadedness	780.4	
Loss of appetite	783.0	
Loss of hair	704	
Loss of memory	780.9	
Loss of taste	781.1	
Low blood pressure (non-specific)	796.3	
Lymphopenia	288.8	
Malaise	780.79	
Memory loss	780.93	
Mood swings	296.99	
Muscle aches/pain	729.1	
Muscle weakness, generalized	780.79	
Myalgia	729.1	
Nasal congestion	478.1	

Symptom	ICD-9 code	Comments
Nausea	787.02	
Nose bleed	784.7	
Nausea and vomiting	787.01	
Nervousness	799.2	
Neutropenia	288	
Night sweats	780.8	
Non-specified injection site	782.99	
Numbness	782.0	
Pain at injection site	782.99	
Pain on urination	788.1	
Pain, abdomen (generalized)	789.0	
Pain, extremity	729.5	
Pain, head (generalized)	784.0	
Pain, joints	719.4	
Pain, lower back	724.2	
Pain, muscle	729.1	
Palpitations	785.1	
Parathesias	782.0	
Pneumaonia	486	
Pruritis	698.9	
Rash	782.1	
Rash at injection site	782.99	
Redness discomfort at injection site	695.99	
Rhinitis	472.0	
Rhinorrhea	478.1	
RUQ discomfort/pain	789.01	
Seizure (not known epilepsy)	780.39	
Sex, decreased or loss of interest	302.71	

Symptom	ICD-9 code	Comments
Shortness of breath	786.05	
Sinus congestion	478.1	
Sinusitis	473.9	
Skin rash	782.1	
Sleep apnea	780.51	
Sleep disturbances (not specified)	780.5	Do not use for insomnia
Sleeplessness	780.52	
Sore throat	462	
Splenomegaly	789.2	
Swelling at injection site	782.99	
Swollen glands	785.6	
Swollen lymph nodes	785.6	
Syncope	780.2	
Taste, loss of	781.1	
Thrombocytopenia	287.5	
Tingling	782.0	
Tiredness	780.79	
Urination, painful	788.1	
Vertigo	780.4	
Visual disturbance (non-specific)	368.9	
Vomiting	787.03	
Weakness, generalized muscle	780.79	
Weight loss (abnormal)	783.2	
Wheezing	786.07	