HALT-C Trial Q x Q

Adverse Event Report

Form #60 Version A: 06/15/2000

Purpose of Form #60: The Adverse Event Report form is used to record information on a single adverse event (definition below). The paper copy of the Adverse Event Report form should be kept in the patient's record for reference and updating. Data entering Form #60 adds the adverse event to a log in the Data Management System (DMS). The information in the adverse event log is used to track adverse events for patient follow-up and reporting purposes.

How to use Form #60: When an adverse event is first data entered, the DMS assigns an event number to it. This number should be recorded on the paper copy of the Adverse Event Report form. Any ongoing adverse event (one with continuing status) must be reviewed with the patient and the status of the particular adverse advent updated at subsequent study visits until the event is resolved. When there is a change in the status of the adverse event, the updated information needs to be recorded on the paper copy and data entered, using the event number to identify the correct adverse event in the DMS. If there is no change in the status of the event, i.e., B5 c, d, e, f, g, and h are exactly the same on a new date, the paper and DMS Form #60 do not need to be updated. A note in the patient's chart indicating that there is no change in this particular adverse event is sufficient source documentation.

When to complete Form #60: The Adverse Event Report form should be completed and data entered whenever coordinators or principal investigators learn of an adverse event. This form may be filled out or updated during a regular study visit or between study visits. When the coordinator checks on the status of a continuing adverse event, the Adverse Event Report form and DMS should be updated with any changes in status and treatment or actions taken as a result. This form should be used from the time the patient signs the Main Trial Screening consent form through Month 54 (M54) for patients in the randomized phase, and Week 72 (W72) for patients in the responder phase.

NOTE ON OTHER FORMS TO BE COMPLETED WHEN AN ADVERSE EVENT OCCURS:

- **Serious Adverse Event Report form (Form #61):** If the adverse event is defined as serious (Question B5d = 3) and is not the first instance of a clinical outcome.
- **Clinical Outcome form (Form #63):** If the adverse event is the first instance of a clinical outcome.
- **Death Report form (Form #64):** If the adverse event is or results in death.
- **Dose Adjustment Logs (Form #28 and Form #29):** If the adverse event results in a dose change.
- **Early Termination of Peginterferon alfa-2a Treatment (Form #19):** If the adverse event results in the premature permanent termination of Peginterferon alfa-2a
- **Early Termination from Trial (Form #25):** If the adverse event results in early termination of the patient's participation in the HALT-C Trial.

SECTION A:

A1. Affix the patient ID label in the space provided.
- If the label is not available, record the ID number legibly.

A2. Enter the patient's initials exactly as recorded on the Trial ID Assignment form.

SECTION B: ADVERSE EVENT INFORMATION

Definition: An adverse event is any adverse change from the patient's baseline (pre-treatment) condition, including intercurrent illness, which occurs during the course of the trial, after treatment has started, whether considered related to treatment or not.

Note on dates:
- All dates in this section should be recorded using MM/DD/YYYY format.
- Enter the 2-digit number for the month in the first 2 spaces provided (i.e., January = "01", February = "02", etc.), the 2-digit number for the day of the month in the second 2 spaces provided, and the 4-digit number for the year in the final 4 spaces provided.

General Instructions for B1 – B4:
These items are entered just once for each adverse event.

B1. As part of a patient's adverse event log, the DMS assigns event numbers sequentially for each patient.
- Record the event number on the paper copy of the Adverse Event Report form.

B2. Enter the event code from the ICD-9 code list. Do not use 799.9. Enter -9 for the code and select "Ignore Value" so that it shows up as a pending edit. If an event code cannot be determined from the ICD-9 Codebook, request a code from the DCC.

B3. Describe the adverse event. One hundred twenty characters (including punctuation and spaces) are available for data entry.

B4. Record the date that the adverse event began.

General Instructions for B5a. – B5h.:
- Complete the first line of this section when the adverse event is first reported. This date may be the same as the date in B4, or a later date, but never an earlier date than B4.
- Complete an additional entry each time the status of the ongoing adverse event is updated with any changes. An entry is required at all study visits until an end date is recorded for the adverse event, and the status is no longer recorded as "continuing".
- If more updates are required than lines available, start a new form #60, using the same information recorded in Sections A and B 1-4.
- All adverse events must be resolved. When a patient is withdrawn from the trial because of death, loss to follow-up, end of participation in the trial (completed W72 of the W20 Responder Phase, completed M54), or other reasons, Form #60 must be completely resolved. See B5c below for details.

B5a. Enter the initials of the person completing this entry in the adverse event log.

B5b. In the first row, record the date that the adverse event was first reported to the clinical center staff, and in subsequent rows, record the date when there is a change in the status of the adverse event that needs updating.
- For new events, record the date the adverse event was first reported.
- For continuing adverse events, record the date the status of the adverse event was changed and reported to the site (e.g., a subsequent study visit or interim phone call).

B5c. Record the date that the adverse event resolved OR for continuing events, check the "ongoing" box.
- Checking "ongoing" implies that the adverse event status (B5g) is "continuing". You must complete B5d through B5h.
- If the patient is no longer in the Trial (loss to follow-up, death, finished W72 / M54) ongoing adverse events need to be resolved.
  - If the patient died, record the date of the death as the date the adverse event resolved and skip to C1.
  - You may choose to record "3" in this space. Place a Form 60 sticker in B5d and skip to C1. Recording a "3" indicates that the patient is medically stable per PI or referred to MD outside the HALT-C Trial.

Form #60 Adverse Event Report
B5c (Rev. 11/01/2003) Date Adverse Event Ended
If ongoing & no longer in study record
3 = medically stable per PI or referred to MD outside HALT-C Trial

B5d. Enter the code that best defines the severity of the adverse event, using the following definitions:

Adverse Event Severity Definitions

1. **Mild**: Discomfort noticed but no disruption of normal daily activity
2. **Moderate**: Discomfort sufficient to reduce or affect normal daily activity
3. **Serious**: Results in death; is life-threatening (immediate risk of death at the time of the event); requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital abnormality or birth defect; or any serious medical condition. Any medical condition, based upon appropriate medical judgement, that may jeopardize the patient and may require medical or surgical intervention will be considered a serious adverse event.

- In addition to this Adverse Event Report, Form #61 Serious Adverse Event Report must also be completed for adverse events rated as serious unless it is the first instance of a clinical outcome.
- Note: "Serious" in B5d is according to the above definition, not because the patient feels the symptom is "serious" to her/him.
- The DCC and Hoffmann-La Roche (for those SAEs that are applicable) must be notified within 24 hours of all serious adverse events.
- If a continuing adverse event that is initially rated as mild or moderate becomes serious, complete a Serious Adverse Event Report form (#61), and notify the DCC and Hoffmann-La Roche (if applicable) within 24 hours.
- If the Form #60 sticker has been placed on the paper, B5d does not have to be completed. Skip to question C1.

B5e. Enter the code that best represents the pattern of this adverse event:

Pattern of Events

1. **Single event:** The event occurred just once, and has resolved at the time of reporting.
2. **Continuous:** The event began just once, and is still ongoing at the time of reporting.
3. **Intermittent:** The event has gone through at least one cycle of starting, stopping, and starting again.

- If the Form #60 sticker has been placed on the paper, B5e does not have to be completed. Skip to question C1.

B5f. Using the definitions on the next page, enter the code for the relationship of the adverse event to trial medication that the patient is currently taking.
- Use code 1, "unrelated", if the patient is not currently taking trial medication (e.g. in the control arm of the trial).
- If the Form #60 sticker has been placed on the paper, B5f does not have to be completed. Skip to question C1.

Relationship of Adverse Event to Trial Medication

1. **Unrelated:** This category is applicable to those adverse events 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.
2. **Remote:** (must have a and b) In general, this category is applicable to an adverse event which meets the following criteria:
   a. It does not follow a reasonable temporal sequence from administration of the Trial medication.
   b. It could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.
   c. It does not follow a known pattern of response to the suspected drug.
   d. It does not reappear or worsen when the drug is re-administered.
3. **Possible:** (must have a and b) this category applies to those adverse events in which the connection with Trial medication administration appears unlikely, but cannot be ruled out with certainty.
   a. It follows a reasonable temporal sequence from administration of Trial medication.
   b. It may have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.
   c. It follows a known pattern of response to the suspected drug.
4. **Probable:** (must have a, b, and c) This category applies to those adverse events which are considered, with a high degree of certainty, to be related to trial medication (either Peginterferon alfa-2a or ribavirin). An adverse event may be considered probable if:
   a. It follows a reasonable temporal sequence from administration of the trial medication.
   b. It could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.
   c. It disappears or decreases on cessation or reduction in dose. There are important exceptions when an adverse event does not disappear upon discontinuation of the drug, yet drug relatedness clearly exists; e.g., 1) bone marrow depression; 2) tardive dyskinesias.
   d. It follows a known pattern of response to the suspected drug.
   e. It reappears upon rechallenge.

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

B5g. Enter the code that best represents the adverse event status. Use the definitions below.

- If the status is "continuing", a record of this will be printed out on the visit control sheet for the patient's next study visit. Check on the status of the adverse event at that point (or sooner, if appropriate) and complete an additional entry in the adverse event log for this event number, only if there are any changes.
- No additional entries may be made in the adverse event log for this event number if the adverse event status is recorded as "resolved, no residual effects", "resolved with sequelae" or "disability". If an adverse event is initially recorded as resolved, but returns, a new adverse event report must be started.
- If the adverse event ends in a death, complete Form #64 Death Report and a Clinical Outcome Report (Form #63). If the patient has died from an event other than this particular adverse event, record "5" death for adverse event status and add a field level comment on paper and in DMS stating: "death not from this adverse event".
- If the Form #60 sticker has been placed on the paper, B5g does not have to be completed. Skip to question C1.

Adverse Event Status Definitions

1. **Resolved, no residual effects:** After the adverse event ends, the patient returns to pre-adverse event status.
2. **Resolved with sequelae:** After the adverse event ends, the patient does not return to pre-adverse event status.
3. **Continuing:** The adverse event is still ongoing at the time of the report.
4. **Disability:** An adverse event that has caused a substantial disruption of the person's ability to conduct normal life functions.
5. **Death:** Death from any cause, not necessarily related to the adverse event itself.

B5h. Enter up to five codes for treatments administered/actions taken to treat the adverse event.

- For continuing adverse events, list only actions taken since the last time an update was data entered.
- Additional therapy is defined as physical therapy, occupational therapy, etc.
- If levels of Peginterferon alfa-2a or ribavirin have been changed, record that here, and on the Peginterferon alfa-2a and Ribavirin Dose Adjustment logs (Forms #28 and #29).
- If hospitalization was required to treat the adverse event, complete Serious Adverse Event Report Form #61, unless this event is the first instance of a clinical outcome.
- If the Form #60 sticker has been placed on the paper, B5h does not have to be completed. Skip to question C1.

SECTION C: FINAL ADVERSE EVENT INFORMATION

C1. If the event code changes during the course of an adverse event, record the new event code (from the ICD-9 code list) here. If the code is the same as when the event started, record the event code from B2. Do not use 799.9. Enter -9 for the code and select "Ignore Value" so that it shows up as a pending edit. If an event code cannot be determined from the ICD-9 Codebook, request a code from the DCC.

C2. If the adverse event description changes during the course of an adverse event, record the new description here. One hundred twenty characters (including punctuation and spaces) are available for data entry. If the description is the same as when the event started, write "same as B3" in the space provided.

For example, at a study visit, the patient reports intermittent headaches. The etiology is unknown. The event is assigned the ICD-9 code 784.0 with a description of "headaches of non-specific etiology." Within the next few days, the patient is diagnosed with a CVA. When you are notified of this event, the form should be updated, and the final adverse event section should be completed. Use the code 436, with a description of "CVA". In this event, a serious adverse event form should also be completed, since CVA would most likely result in a hospitalization and be considered medically significant in the opinion of the investigator.