HALT-C Trial Q x Q

Serious Adverse Event Report

Form #61 Version B: 08/20/2001 (Revised 03/05/2003)

Purpose of Form #61: The Serious Adverse Event Report form is used to record information on a serious adverse event. Hoffmann-La Roche uses this report for determining whether an event is unexpected and related to study drug(s). Only some of this information is to be data entered. All sections outlined by a broken line are for Hoffmann-La Roche and not for data entry purposes.

Definition: A **serious adverse event** is any untoward medical occurrence that:

- Results in death,
- Is life-threatening (there is a 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**
- 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 outcomes listed above.

- **The first instance of a clinical outcome 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.

Reporting procedures / When to complete Form #61: All serious adverse events occurring to any participant in the HALT-C Trial (Screening, Lead-in, Treatment, Control, Week 20 Responders) up until Study Visit Month 54 (M54) must be reported via fax and a telephone call within 24-48 hours of learning of the event using whatever information is available to:

- Margaret C. Bell at the Data Coordinating Center, New England Research Institutes, Inc.

And if applicable, send SAE Form #61 also to:

- Dr. Cliff Joseph at Hoffmann-La Roche.
  - Do not send the following types of SAEs to Hoffmann-La Roche
    - Control patients off drug for at least 12 weeks.
    - Elective surgery.
    - Any clinical outcomes.

Contact information for the DCC and Hoffmann-La Roche is listed at the end of this QxQ.

Relationship to Adverse Event Report (Form #60): Form #60 Adverse Event Report must be entered into the Data Management System (DMS) prior to Form #61 Serious 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.

How to fill out Form #61 on paper: Any section or question on Form #61 that is outlined with a dotted line is information needed by Hoffmann-La Roche, but is not data entered.

If the SAE has resolved (no longer continuing or unknown) when you complete Form #61, then the paper form only needs to be completed once and data entered.

Another Form #61 must be completed when additional information regarding a serious adverse event becomes available. It is likely that some of the information that must be collected about serious adverse events will not be available at the time the Serious Adverse Event Report form is initially faxed to the DCC. In general, only two SAE Forms will be filled out per patient: one when the site is notified of the SAE, and the second when the SAE is resolved.

If the SAE has not resolved (either continuing or unknown), then you will need to complete an initial paper Form #61 with current information. When more information is received, 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.

How to Data Enter Form #61: The information on Form #61 is very important to the HALT-C Trial and should have priority for data entry. Data entry of Form #61 is different than other HALT-C forms in the DMS. Any questions regarding how to data enter Form #61 should be addressed to the DCC Data Management Team.

- There may be multiple paper Form #61s for the same patient with the same event code, but there is only one Form #61 in the DMS corresponding to this patient and particular event.
- Some data on the paper form does not need to be data entered. Any information outlined with a dotted line is for Hoffmann-La Roche's information only and is not to be data entered and is so noted on the paper form.
- The DCC prepares a monthly report to the DSMB using the information data entered on this form. In order for the DSMB report to be accurate, changes to Form #61 must be carefully data entered in the DMS in a timely manner and spelling must be accurate. Please do not enter using all CAPITAL LETTERS. Use sentence case.

SECTION A: GENERAL INFORMATION

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 two spaces provided (i.e., January = "01", February = "02", etc.), the 2-digit number for the day of the month in the second two spaces provided, and the 4-digit number for the year in the final four spaces provided.

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.

A3. Enter event number assigned by the DMS when Form #60 Adverse Event Report is data entered for this serious adverse event.

A4. Enter the initials of the person completing the form.

A5. Record the date this form was initially completed. This date may be different than the date the SAE occurred, as the patient may not report this event at the time it occurs. This date can never be before the SAE occurred.

A6. Record the date the form was updated with additional information. If this is the first time the form is being filled out for this event, write in the same date recorded for question A5.

A7. If this is the first serious adverse event ever reported for this patient, answer "Yes". For every subsequent serious adverse event reported for this patient, answer "No".

SECTION B: PERSONAL DATA ***(Not to be data entered)***

B1. Record the patient's date of birth using the MM/DD/YYYY format. This information should be the same as question B1 reported on Form #1.

B2. Make a check in the box next to the patient's gender.

B3. From the code box provided, record the patient's race. If "other" race, please specify.

B4. Record the patient's weight in kilograms or pounds. Do not answer both. This weight can come from the most recent Form #11 question B1 if a more recent weight is not available from the patient's chart.

B5. Record the patient's height in centimeters or inches. Do not answer both. This height can come from the W00 Form #11 question B2 if a more recent height is not available from the patient's chart.

SECTION C: SERIOUS ADVERSE EVENT

C1. 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.

C2. Enter the serious adverse event description. 60 characters (including punctuation and spaces) are available for data entry. This description can be very brief (i.e. left bundle branch block, possible MI, fever of unknown origin).
- If the description is cellulitis, indicate if it is related to injection site.
- If description is procedure related, indicate which procedure (i.e. RUQ pain, post liver bx).

C3. Record the date that the serious adverse event began using the MM/DD/YYYY format.

SECTION D: SERIOUSNESS

D1. Indicate why this event is considered serious. Up to four responses may be chosen.
- Choose answer "1" to indicate an intervention that was taken to prevent answers "2"-"7" from occurring.
- Life threatening means there is a risk of death at the time of the event.
- Choose answer "8", "None of the above, but it is medically significant in the opinion of the investigator", **only** if no other answer was chosen.

SECTION E: OUTCOME OF SERIOUS ADVERSE EVENT

E1. Using the definitions below, circle one answer that best describes this adverse event at the time this form is being completed.
- If outcome is "Resolved, with no residual effects" or "Resolved, with sequelae", skip to E4.
- If outcome is "Continuing", "Disability", or "Unknown", skip to Section F.
- If outcome is "Death", continue to E2.

Adverse Event Outcome 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:** An adverse event, which results in death.

E2. Enter the date of death using the MM/DD/YYYY format.

E3. Enter the cause of death. Seventy-five characters (including punctuation and spaces) are available for data entry. Skip to Section F.

E4. Enter the date the adverse event was resolved using the MM/DD/YYYY format.

Guidelines for determining when a serious adverse event is resolved and the resolution date:

- Defining the resolution date of a serious adverse event is generally the date the acute event was over. E.g., a patient who has appendicitis and has an appendectomy performed on April 1, 2002, would have a resolution date of 04/01/2002. A patient who was newly diagnosed with diabetes who was hospitalized and discharged on March 17, 2002 with medications to control diabetes would have a resolution date of 03/17/2002.

- A patient who is hospitalized for suicidal ideation and depression who subsequently is discharged from the hospital with medications and no longer having suicidal ideation would have a resolution date with sequelae (now the patient is on medications) of the discharge date from the hospital.

SECTION F: PEGINTERFERON ALFA-2A

F1. Circle "Yes" if the patient has taken **any** Peginterferon alfa-2a for the HALT-C Trial and continue to F2. If the patient has never taken any Peginterferon alfa-2a for the HALT-C Trial, circle “No” and skip to Section G.

F2. Enter the date the patient began taking Peginterferon alfa-2a using the MM/DD/YYYY format.

F3. Enter the dose of Peginterferon alfa-2a the patient was taking at the time of the SAE, in mcg.

F4. Using the tables on the last page of this QxQ, enter the code for the relationship of the adverse event to Peginterferon alfa-2a.

F5. Enter if the dose of Peginterferon alfa-2a has been adjusted in response to this SAE.
- If the patient was already on an adjusted dose at the time of the SAE, and no further adjustments were made, answer “no” and skip to section G.
- If no adjustment was made in response to this SAE, answer “no” and skip to section G.

(Not to be data entered)

F6. If Peginterferon alfa-2a was altered in response to this SAE, check the box that applies:
- If dose was lowered, record the date it was lowered using the MM/DD/YYYY format. Record the lowered dose in mcg.
- If dose was interrupted, record the date it was stopped. Record the date it was restarted. If the dose was discontinued, record the date stopped.

SECTION G: RIBAVIRIN

G1. Circle "Yes" if the patient has taken **any** Ribavirin for the HALT-C Trial and continue to G2. If the patient has never taken Ribavirin for the HALT-C Trial, circle “No” and skip to Section H.

G2. Enter the date the patient began taking Ribavirin using the MM/DD/YYYY format.

G3. Enter the total daily dose of Ribavirin the patient was taking at the time of the SAE, in mg.

G4. Using the tables on the last page of this QxQ, enter the code for the relationship of the adverse event to Ribavirin.

G5. Enter if the dose of Ribavirin has been adjusted in response to this SAE.
- If the patient was already on an adjusted dose at the time of the SAE, and no further adjustments were made, answer “no” and skip to section H.
- If no adjustment was made in response to this SAE, answer “no” and skip to section H.

(Not to be data entered)

G6. If Ribavirin was altered in response to this SAE, check the box that applies:
- If dose was lowered, record the date it was lowered. Record the lowered dose in mg.
- If dose was interrupted, record the date it was stopped. Record the date it was restarted.
- It the dose was discontinued, record the date stopped.

SECTION H: CONCOMITANT MEDICATIONS ***(Not to be data entered)***

H1. Check the "Yes" box if the patient was taking any other medications at the time of the SAE. Check "No" box if the patient was taking no medications at the time of the SAE and skip to section I.

H2. Using the table, enter all the concomitant medications the patient was taking.

H2a. Write in the name of the medication.

H2b. Write in the total daily dose and units (mg, mcg, ml, etc.).
- For example, if a patient is taking 600 mg of Motrin every morning, write in “600 mg”.
- If the patient is taking 500 mg of amoxicillin TID, write in “1500 mg”.

H2c. Using the tables on page 9 of this QxQ, check off the box if there is a suspected relationship between the concomitant medication and the SAE.

H2d. Enter the date the patient began taking this medication using the MM/DD/YYYY format. If the month and/or day are not known, write “DK” in the month and/or day section and record the year.

H2e. Check off the box if this medication is ongoing. If ongoing, skip to next medication or Section I. If discontinued, answer question H2f.

H2f. Enter the date the patient stopped taking this medication using the MM/DD/YYYY format. If the month and/or day are not known, write “DK” in the month and/or day section and record the year.

SECTION I: SERIOUS ADVERSE EVENT DESCRIPTION

Two parts in Section I describe the Serious Adverse Event. The first section should be written as an ongoing progress note in a medical chart with the date and what is happening at that time. The second section should be completed when the final status of the serious adverse event is known.

I1. This section should be written as an ongoing progress note in a medical chart. Summarize the event. Please start with the date: (e.g. 3/12/01 Pt’s wife telephoned to report that pt complained of chest pain and went to ER on 3/15/01 where he was worked up for possible MI. He is still in hospital. Study drugs stopped on 3/15/01. Will follow.) Up to 3,000 characters (including punctuation and spaces) are available for data entry. If the SAE status is complete, record N/A or –1 and complete section I2.

I2. This section should be completed when the final status of the Serious Adverse Event is known. If the serious adverse event is continuing or unknown, enter -9 and select “Ignore Value” so that it shows up as a pending edit.

Summarize the serious adverse event, including dates of hospitalization and severity if appropriate. Include relevant drug history and outcomes. This final summary will be used to report to the FDA and DSMB, and should be succinct and thorough with correct spelling and grammar. Remember you are writing this summary for a clinician who does not have access to the patient’s history or medical chart. Do not use physician or institutional names. The DSMB wants to know if this patient is being treated appropriately and if the drug was appropriately reduced or stopped. Up to 3,000 characters (including punctuation and spaces) are available for data entry.

The DCC sends the DSMB monthly SAE reports. SAE information needs to be data entered within a week of sending the report to the DCC. At the quarterly DSMB meetings, decisions are made as to what needs to be recorded in Sections I1 and I2. As of March 2004, the following are required:

1. All cardiac and/or pulmonary SAEs (i.e., syncope, SOB, chest pain, etc.) should have Hgb from W00 and time of SAE in the final summary (I2).
2. All infectious SAEs should include a report of the WBC and the ANC from W00 and time of SAE in the final summary (I2).
3. All "bleeding" SAEs should include a report of the platelet count from W00 and time of SAE in the final summary (I2).
4. All cellulitis SAEs should include the site/location, especially in relation to the injection site in the final summary (I2).
5. All depression SAEs should include information of any previous history of depression or other mental conditions in the final summary (I2).
6. Indicate if a patient has a history of cardiac disease, diabetes, or other significant medical history.

Example 1: Pt. with hx of hypertension and diabetes had sx of chest pain. Admitted via ER to hospital for cardiac work-up. EKG, blood tests, and stress tests all within normal limits. Psych consult revealed dx of acute anxiety. Will be followed by psychiatrist. Was put on Xanax prn. Hgb W00: 14.6. Hgb at time of SAE: 11.2.

Example 2: Pt had cough and fever. Admitted to hospital through ER. Chest x-ray revealed LLL pneumonia. Cultures revealed organism: S. pneumoniae and Legionella spp. IV antibiotics given. W00 ANC: 2.4; WBC: 70; at time of admission ANC: 5.9; WBC: 200. Pt discharged from hospital. She is currently on oral antibiotics and doing well with no more cough and fever. Follow-up with pulmonary MD.

SECTION J: TREATMENT/PROCEDURES FOR SAE ***(Not to be data entered)***

J1. Check "Yes" box if any treatments were given or procedures were performed to treat this SAE. Check "No" box if no treatments were given or procedures were performed and skip to section K.

J1a. Write in the treatment (including medications and other therapies) or procedures (including surgery) that were initiated to treat this condition

J1b. Enter the date the patient began this treatment or procedure using the MM/DD/YYYY format.

J1c. Check "Ongoing" box indicating if treatment is ongoing.

J1d. Enter the date the patient stopped this treatment or procedure using the MM/DD/YYYY format.

SECTION K: RELEVANT LABORATORY AND DIAGNOSTIC TESTS ***(Not to be data entered)***

K1. Check "Yes" box if any relevant laboratory or diagnostic tests were done for this SAE. Check "No" box if no relevant laboratory or diagnostic tests were done and skip to section L.

K1a. Write in the test name.

K1b. Enter the date the test was performed using the MM/DD/YYYY format.

K1c. Check "Result pending" box indicating if the result is pending. Skip to the next line or to Section L.

K1d. Write in the test result.

K1e. Write in the normal value, or value range for this test.

- For laboratory tests such as hematology and chemistries, you may write in the laboratory provided ranges for normal.
- For a diagnostic test, such as an ultrasound, you may write in the term “normal”.

SECTION L: RELEVANT MEDICAL HISTORY ***(Not to be data entered)***

L1. Check "Yes" box if there is any medical history relevant to, or associated with, this SAE. Check "No" box if there is no medical history relevant to or associated with this SAE and skip to section M.

L1a. Indicate the disease or surgical procedure associated with this event.

L1b. Enter the disease start date or the date of surgery using the MM/DD/YYYY format. If the month and/or day is not known, write “don’t know” or “DK” in the month and/or day section and record the year.

L1c. Check the "Ongoing" box indicating if the relevant medical history is ongoing. Skip to the next line or section M.

- If the patient no longer has the disease, do not check the "Ongoing" box and continue to L1d.
- If the event was a surgery, do not check the "Ongoing" box and continue to L1d.

L1d. If the event was a disease, record the end date of the disease using the MM/DD/YYYY format.

- If the month and/or day are not known, write or “DK” in the month and/or day section and record the year.
- If the event was a surgery, write “not applicable” or “N/A” in the space provided.

SECTION M ***(Not to be data entered)***

The PI, or his/her designee must complete the information requested in this box, and sign and date the form. Hoffmann-La Roche will use this contact information to follow-up on any information they may need to know to determine the relationship of the serious adverse event to the trial medication.

SOURCE DOCUMENTS AND MAILING INFORMATION:

Form #61 Serious Adverse Event Report must be completed and faxed to the DCC within 24-48 hours. **Do not send copies of any source documents** unless Hoffmann-La Roche notifies your site and requests such documentation. If the site needs to send source documentation, black out all identifying patient information, such as name and medical record number, and replace with the patient ID number (labels provided by the DCC may be used).

DCC Contact Information

Contact:	Margaret C. Bell, RN
Phone:	(617) 923-7747 x522
Fax:	(617) 926-0144
E-mail:	mbell@neri.org
Address:	New England Research Institutes, Inc. 9 Galen Street Watertown, MA 02472

Hoffmann La-Roche Contact Information

Contact:	Cliff Joseph, MD
Phone:	(973) 562-3613
Fax:	(973) 562-3602
E-mail:	cliff.jospeh@roche.com
Address:	Hoffmann-La Roche 340 Kingsland St, Bldg 85, 2W03 Nutley, NJ 07110

TABLES FOR RELATIONSHIP OF ADVERSE EVENTS TO PEGINTERFERON ALFA-2A, RIBAVIRIN, OR CONCOMITANT MEDS

Use these tables to determine if the SAE was related to Peginterferon alfa-2a, Ribavirin, or any concomitant medications the patient was taking.

Relationship of Adverse Event to Trial and Concomitant Medications

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 first two) 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 drug.
   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 first two) this category applies to those adverse events in which the connection with the drug administration appears unlikely, but cannot be ruled out with certainty.
   a. It follows a reasonable temporal sequence from administration of the drug.
   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 first three) this category applies to those adverse events that are considered, with a high degree of certainty, to be drug related. An adverse event may be considered probable if:
   a. It follows a reasonable temporal sequence from administration of the drug.
   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 barrow 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 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	-	-	-	+