HALT-C Trial Q X Q
Central Death Review
Form # 964 and Worksheet Version A: 01/09/2009

Purpose of Form #964: This form is used to document the central evaluation of reported deaths during or after the randomized phase in HALT-C Trial randomized patients.

When to complete Form #964: This form will be completed for each randomized patient death that occurred on or before March 31, 2009.

A DCC staff person will complete the Form #964 based on information provided by the central review committee. A DCC staff person will data enter Form #964 into the HALT-C Data Management System (DMS). Forms will be kept on file at the DCC.

Note on dates:
- All dates in this form 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.

FORM #964 WORKSHEET

Reported deaths will be reviewed by a central committee consisting of a group of HALT-C Trial Investigators. Each member will receive an information packet about a death. The packet will include:

- A Worksheet of Form #964.

- A blinded copy of the Death Summary information produced by the HALT-C Data Management System based upon information completed by the clinical center staff and the clinical investigator at the reporting clinical center where the patient was last followed.

Each reviewer will individually review documentation and complete a Worksheet to be submitted to the DCC for central review determination. Instructions for each question are provided below.

Each Reviewer will return his/her Worksheet to the DCC by fax or by Federal Express. The DCC will notify the Reviewer via email upon receipt.

DCC Contact Information

Contact:	Kristin K. Snow
Address:	HALT-C Data Coordinating Center New England Research Institutes 9 Galen Street Watertown, MA 02472
Phone:	(617) 923-7747 ext. 292
Secure Fax:	(617) 673-9526

WORKSHEET SECTION A: GENERAL INFORMATION

A1. Enter the Clinical Outcome number assigned to the death.

A2. Enter the initials of the Reviewer as shown in the table below.

Herbert L. Bonkovsky	HLB	Jay H. Hoofnagle	JHH
Adrian M. Di Bisceglie	AMD	Chihiro Morishima	C M
Jules L. Dienstag	JLD	Leonard B. Seeff	LBS

A3. Enter the date of the review using MM/DD/YYYY format.

WORKSHEET SECTION B: REVIEWER DETERMINATION

Causality Codes		
Causality score	*Likelihood*	*Description*
Definite or highly likely	≥ 75%	The evidence for causality is “beyond a reasonable doubt” or “clear and convincing”.
Probable	50 to 74%	The causality is supported by “the preponderance of the evidence” but the evidence cannot be considered definite or highly likely.
Possible	25 to 49%	The causality is not supported by “the preponderance of the evidence”; however, one cannot exclude the possibility.
Unlikely	< 25%	The evidence for causality is “highly unlikely” based upon the available information.

B1. Based on the information provided, the reviewer will determine the primary cause of death and circle one answer. If the answer is “Other known cause”, the reviewer will specify an answer.

B2. Based on the information provided, the reviewer will determine if hepatitis C related liver disease was a contributing cause of death. The reviewer will circle one answer. If the answer is “Yes”, the reviewer will answer Question B2a. If the answer is “No”, the reviewer will skip to question B3.

B2a. The reviewer will determine the likelihood that hepatitis C related liver disease was a contributing cause of death according to the Causality Codes in the box above. The reviewer will circle one answer.

B3. Based on the information provided, the reviewer will determine if interferon-therapy was a contributing cause of death and circle one answer. Last dose of interferon must be within 3 months of the date of death to be considered interferon-related. If the answer is “Yes”, the reviewer will answer Question B3a. If the answer is “No”, the Worksheet is complete.

B3a. Based on the information provided, the reviewer will determine the likelihood that interferon therapy was a contributing cause of death according to the Causality Codes in the box above. The reviewer will circle one answer. Last dose of interferon must be no greater than 3 months after the date of death to be considered interferon-related. The Worksheet is complete.

FORM #964 CENTRAL REVIEW FORM AGREEMENT

The DCC will collect a Worksheet completed for each case from each reviewer. The DCC will review the Worksheets and determine if there is agreement according to the following definitions.

“Perfect agreement” is defined as unanimous agreement on Question B1 (primary cause of death), Questions B2 and B2a (was hepatitis C a contributing cause), and Questions B3 and B3a (was interferon therapy a contributing cause).

“Agreement” on Question B1 is defined as follows: If a majority of reviewers agree on a primary cause of death, then the final code will be the most commonly selected code.

“Agreement” on Questions B2 and B2a and Questions B3 and B3a is defined as follows: if all members grade the likelihood >= 50%, there is “agreement”. If all members grade the likelihood >= 50% but some say definitely and some say possibly, then the final code will be the most commonly selected code. Similarly, if all members grade the likelihood < 50%, there is “agreement”. If all members grade the likelihood < 50% but some say possibly and some say unlikely, then the final code will be the most commonly selected code.

For the cases with "perfect agreement" or “agreement”, no further review is needed. The DCC will complete the Central Review Form #964 and enter into the DMS.

For the cases where there is lack of agreement or in the event of a tie vote, the central review committee will meet in person or by teleconference to discuss the case and to centrally determine the answers to record on Form #964. The DCC will send copies of all available source documents to Reviewers in preparation for the conference call or meeting. The packet will include:

- A Worksheet of Form #964.
- A blinded copy of the Death Summary information produced by the HALT-C Data Management System based upon information completed by the clinical center staff and the clinical investigator at the reporting clinical center where the patient was last followed.
- Blinded copies of source documents provided by the reporting clinical center, if available.

The reviewers will consider the following levels of evidence when reviewing:

- Highest levels of evidence
  - Case summary from hospitalization
  - Autopsy report
  - Information provided by PI and site investigators
- Lesser levels of evidence
  - Death certificate
  - Any other information

FORM #964 CENTRAL REVIEW FORM

SECTION A: GENERAL INFORMATION

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 the date of the central review using MM/DD/YYYY format.

A4. Enter the number of reviewers who reviewed the case.

A5. Enter the Clinical Outcome number assigned to the death. Clinical Outcome numbers are assigned in sequential order automatically by the DMS upon data entry of Form #63. The Clinical Outcome Number must be written in the box at the top of each subsequent page of Form #964.

SECTION B: CENTRAL REVIEW DETERMINATION

B1. The DCC staff person will circle one answer for the primary cause of death, as determined by the group. The DCC staff person will circle one answer. If the answer is "Other known cause", the answer specified by the group will be recorded

B2. The DCC staff person will circle one answer for whether hepatitis C related liver disease was considered a contributing cause of death, as determined by the group. If the answer is "Yes", go to Question B2a. If the answer is "No", skip to question B3.

B2a. The DCC staff person will circle one answer for the likelihood that hepatitis C related liver disease was a contributing cause of death, as determined by the group.

B3. The DCC staff person will circle one answer for whether interferon therapy was considered a contributing cause of death, as determined by the group. Last dose of interferon must be within 3 months of the date of death to be considered interferon-related. If the answer is "Yes", go to Question B3a. If the answer is "No", the form is complete.

B3a. The DCC staff person will circle one answer for the likelihood that interferon was a contributing cause of death, as determined by the group.