Dataset Integrity Check (DSIC) for the Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) Trial Data Files

Prepared by

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Revision History

Version	Author/Title	Date	Comments
1.0	Norma Pugh	4 April 2012	

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1 Study Background

All SAS data files, as provided by the Data Coordinating Center (DCC), are located in the HALT-C Data folder in the Official Archive. For this replication, all variables were taken from the Dienstag_2011_chc SAS data file, which will be located in the Official Archive.

Published data on the incidence of liver disease progression among subjects with histologically advanced but compensated chronic hepatitis C is limited. Most data have been obtained from small, single-center studies, without protocol-driven systematic data collection. Based on such reports, the annual incidence of progression to hepatic decompensation in compensated cirrhosis has been estimated to be approximately 6% (range, 4%-8%) [1].

The HALT-C Trial is a randomized, double-blind, placebo-controlled trial conducted at ten U.S. centers. The trial aims to study the rate of liver disease progression among patients who did not clear virus on peginterferon and ribavirin therapy. 1,050 subjects were followed for 3.5 years on maintenance peginterferon treatment and were subsequently followed off therapy.

Dienstag et al. report that among patients with advanced hepatitis C who failed peginterferon and ribavirin therapy, the rate of liver-related outcomes, including death and liver transplantation, is high, particularly once the Child-Turcotte-Pugh (CTP) score (the most common first outcome) is ≥ 7 [1].

The intent of this DSIC is to provide confidence that the data distributed by the NIDDK repository is a true copy of the study data. Our intent is not to assess the integrity of the statistical analyses reported by study investigators. As with all statistical analyses of complex datasets, complete replication of a set of statistical results should not be expected on a first (or second) exercise in secondary analysis. This occurs for a number of reasons including differences in the handling of missing data, restrictions on cases included in samples for a particular analysis, software coding used to define complex variables, and other factors. Experience suggests that most discrepancies can ordinarily be resolved by consulting with the study data coordinating center (DCC); however, this process is labor-intensive for both DCC and Repository staff. Therefore, it is not our policy to resolve every discrepancy observed in an integrity check. Specifically, we do not attempt to resolve minor or inconsequential discrepancies with published results or discrepancies that involve complex analyses unless NIDDK Repository staff suspect that the observed discrepancy suggests that the dataset may have been corrupted in storage, transmission, or processing by repository staff. We do, however, document in footnotes to the integrity check those

instances in which our secondary analyses produced results that were not fully consistent with those reported in the target publication

2 Archived Datasets

All SAS data files, as provided by the Data Coordinating Center (DCC), are located in the HALT-C Data folder in the Official Archive. For this replication, all variables were taken from the Dienstag_2011_chc SAS data file, which will be located in the Official Archive.

3 Statistical Methods

Analyses were performed to duplicate results for the data published by Dienstag et al [1] in *Hepatology* in August 2011. Because maintenance peginterferon treatment did not alter liver disease progression, treated and control patients were analyzed together [1].

Frequencies of total clinical outcomes and first outcome were computed, by stage of histologic fibrosis (Tables B - D). The annualized incidences of clinical outcomes were computed from Kaplan-Meier life-table estimates (Tables F - H). 7-year cumulative event rates were divided by 7. The SAS code for our tabulations is included in Attachment 1.

4 Results

Table 1 in the publication [1], Frequency of Total Clinical Outcomes and First Outcome, by Stratum, reports on clinical and histological outcomes, by stage of histologic fibrosis. Our Table A lists the variables we used in our replication and Tables B - D compare the results calculated from the archived data file to the results published in Table 1. The results of the replication agree with published results.

The annualized incidence of each clinical outcome is reported by baseline stage of fibrosis and following CTP Score ≥ 7 (Table 2), by sex and age (Table 3) and by baseline platelet count (Table 4). Our Table E lists the variables used in our replication and Tables F - H compare selected results calculated from the archived data file to the results published in Tables 2, 3 and 4. Again, the results of the replication are similar to published results.

5 Conclusion

The NIDDK repository is confident that the HALT-C data files to be distributed are a true copy of the study data.

6 References

1. Dienstag JL, et al. (2011) A Prospective Study of the Rate of Progression in Compensated, Histologically Advanced Chronic Hepatitis C. Hepatology; 54(2): 396-405. (http://www.ncbi.nlm.nih.gov/pubmed/21520194)

Table A: Variables Used to Replicate Table 1, Frequency of Total Clinical Outcomes and First Outcome, by Stratum.

Table Variable	Variables Used in Replication
Stage of histologic fibrosis	cirrhosis (0 = fibrosis, 1 = cirrhosis)
All death	dth_a; first_out_every = 1
Liver-related death	liverdeath; first_out_every
Liver transplantation	trans_a; first_out_every = 9
Liver-related death or liver transplantation	liverdeath_trans; first_out_every
HCC or presumed HCC	hcc_phcc_a; first_out_every = 2 or 8
CTP score ≥ 7 on two consecutive visits	ctp_a; first_out_every = 3
Variceal hemorrhage	vh_a; first_out_every = 4
Ascites	asc_a; first_out_every = 5
Bacterial peritonitis	bper_a; first_out_every = 6
Encephalopathy	ence_a; first_out_every = 7

Table B: Comparison of Values Computed in Integrity Check to Reference Article Table 1 Values Stratum = Fibrosis.

Characteristic	Total Number of Outcomes			First Outcome		
	Dienstag	Integrity Check	Difference	Dienstag	Integrity Check	Difference
All death	49	49	0	24	24	0
Liver-related death	27	27	0	5	5	0
Liver transplantation	30	30	0	2	2	0
Liver-related death or liver transplantation	54	54	0	7	7	0
HCC or presumed HCC	40	40	0	35	35	0
CTP score ≥ 7 on two consecutive visits	49	49	0	36	36	0
Variceal hemorrhage	9	9	0	5	5	0
Ascites	34	34	0	12	12	0
Bacterial peritonitis	6	6	0	0	0	0
Encephalopathy	18	18	0	8	8	0
Total*	235 outcomes	235 outcomes	0	122 patients	122 patients	0

Each patient could be counted more than once.
*All-cause death + liver transplantation + HCC or presumed HCC + CTP score ≥7 + variceal hemorrhage + ascites + bacterial peritonitis + encephalopathy.

Table C: Comparison of Values Computed in Integrity Check to Reference Article Table 1 Values Stratum = Cirrhosis.

Characteristic	Total Number of Outcomes			First Outcome		
	Dienstag	Integrity Check	Difference	Dienstag	Integrity Check	Difference
All death	89	89	0	29	29	0
Liver-related death	55	55	0	5	5	0
Liver transplantation	56	56	0	2	2	0
Liver-related death or liver transplantation	103	103	0	7	7	0
HCC or presumed HCC	48	48	0	32	32	0
CTP score ≥ 7 on two consecutive visits	121	121	0	101	101	0
Variceal hemorrhage	18	18	0	10	10	0
Ascites	67	67	0	23	23	0
Bacterial peritonitis	3	3	0	0	0	0
Encephalopathy	42	42	0	10	10	0
Total*	444 outcomes	444 outcomes	0	207 patients	207 patients	0

Each patient could be counted more than once.
*All-cause death + liver transplantation + HCC or presumed HCC + CTP score ≥7 + variceal hemorrhage + ascites + bacterial peritonitis + encephalopathy.

Table D: Comparison of Values Computed in Integrity Check to Reference Article Table 1 Values Stratum = Total .

Characteristic	Total Number of Outcomes			First Outcome		
	Dienstag	Integrity Check	Difference	Dienstag	Integrity Check	Difference
All death	138	138	0	53	53	0
Liver-related death	82	82	0	10	10	0
Liver transplantation	86	86	0	4	4	0
Liver-related death or liver transplantation	157	157	0	14	14	0
HCC or presumed HCC	88	88	0	67	67	0
CTP score ≥ 7 on two consecutive visits	170	170	0	137	137	0
Variceal hemorrhage	27	27	0	15	15	0
Ascites	101	101	0	35	35	0
Bacterial peritonitis	9	9	0	0	0	0
Encephalopathy	60	60	0	18	18	0
Total*	679 outcomes	679 outcomes	0	329 patients	329 patients	0

Each patient could be counted more than once.
*All-cause death + liver transplantation + HCC or presumed HCC + CTP score ≥7 + variceal hemorrhage + ascites + bacterial peritonitis + encephalopathy.

Table E: Variables Used to Replicate Tables 2, 3 and4, Annualized Incidence of Each Clinical Outcome (by selected covariates).

Table Variable	Dataset/Variables Used in Replication
Stage of histologic fibrosis	cirrhosis (0 = fibrosis, 1 = cirrhosis)
CTP score ≥ 7	ctp_a (0 = no, 1 = yes)
Sex	female (0 = no, 1 = yes)
Age	age50 (0 = <50 years, 1 = ≥50 years)
Baseline platelet count	pltcate_a (1:<100, 2:100-<150, 3:150-<200, 4:200+)
Variceal hemorrhage	vh_life_year_a; vh_a (0 = no, 1 = yes)
Ascites	asc_life_year_a; asc_a (0 = no, 1 = yes)
All death	dth_life_yeara_a; dth_a (0 = no, 1 = yes)
Liver-related death or liver transplantation	liverdeath_trans_year; liverdeath_trans (0 = no, 1 = yes)

Table F: Comparison of Values Computed in Integrity Check to Reference Article Table 2 Values.

Characteristic	Stratum = Fibrosis			Stratum = Cirrhosis			Events After CTP Score ≥7		
	Dienstag	Integrity Check	Difference	Dienstag	Integrity Check	Difference	Dienstag	Integrity Check	Difference
Variceal hemorrhage	0.2 %	0.3%	+0.1	0.9%	0.9%	0	1.2%	1.8%	+0.6
Ascites	1.0%	1.0%	0	2.9%	2.9%	0	12.7%	11.6%	-1.1
All death	1.7%	1.5%	-0.2	3.9%	3.9%	0	10.0%	10.6%	+0.6
Liver-related death or liver transplantation	1.6%	1.6%	0	4.2%	4.2%	0	14.3%	16.4%	+1.9

Table G: Comparison of Values Computed in Integrity Check to Reference Article Table 3 Values.

Characteristic	Male			Female			<50 years			≥50 years		
	Dienstag	IC	Difference	Dienstag	IC	Difference	Dienstag	IC	Difference	Dienstag	IC	Difference
Variceal hemorrhage	0.5%	0.5%	0	0.6%	0.4%	-0.2	0.6%	0.6%	0	0.4%	0.4%	0
Ascites	1.7%	1.7%	0	1.8%	1.8%	0	1.9%	1.9%	0	1.6%	1.5%	-0.1
All death	2.4%	2.4%	0	2.6%	2.7%	+0.1	2.0%	2.1%	+0.1	2.9%	2.9%	0
Liver-related death or liver transplantation	2.8%	2.8%	0	2.3%	2.1%	-0.2	2.4%	2.5%	+0.1	2.9%	2.9%	0

Table H: Comparison of Values Computed in Integrity Check to Reference Article Table 4 Values.

Characteristic	Platelet Count <100			Platelet Count 100 to <150			Platelet Count 150 to <200			Platelet Count ≥200		
	Dienstag	IC	Difference	Dienstag	IC	Difference	Dienstag	IC	Difference	Dienstag	IC	Difference
Variceal hemorrhage	1.3%	1.3%	0	0.4%	0.4%	0	0.2%	0.2%	0	0.2%	0.3%	+0.1
Ascites	4.8%	4.7%	-0.1	2.2%	2.3%	+0.1	0.9%	1.1%	+0.2	0.5%	0.5%	0
All death	5.3%	5.5%	+0.2	2.6%	2.7%	+0.1	1.9%	2.1%	+0.2	1.0%	1.3%	+0.3
Liver-related death or liver transplantation	6.4%	6.4%	0	2.9%	3.0%	+0.1	1.8%	2.1%	+0.3	0.5%	0.9%	+0.4

Attachment A: SAS Code

```
options errorabend nofmterr;
/*******************************************************************************/
/*
/* Program: R:\05_Users\Norma\HALT-C\table1.sas
/* Author:  Norma Pugh
/* Date:    January 2012
/* Purpose: Replicate table 1 results.
/*
/*******************************************************************************/
/* DATA SOURCE */
libname data
'\\rcdubuntu01.rtp.rti.org\niddk\03_Data_And_Tools\Studies\HALT_C\Official_Archive\v3.0\HALT-C
Data\Analysis dataset\Publication_datasets';

/**************************/
/* DEFINE ANALYSIS DATASET */
/**************************/
data table1;
 set data.Dienstag_2011_chc;
run;


/*****************************/
/* REPLICATE ANALYSIS RESULTS */
/*****************************/
/* Frequency of Total Clinical Outcomes, by Stratum */
title'Frequency of Total Number of Outcomes, by Stratum';
proc freq data=table1; tables cirrhosis*(dth_a liverdeath trans_a liverdeath_trans hcc_phcc_a
ctp_a vh_a asc_a bper_a ence_a) / list missing; run;


/* Frequency of First Outcome, by Stratum */
title'Frequency of First Outcomes, by Stratum';
proc freq data=table1; tables cirrhosis*(first_out_every) / list missing; run;
title2'Liver-related death or Liver transplantation';
proc freq data=table1; tables cirrhosis*first_out_every*liverdeath*liverdeath_trans / list
missing nopct; run;
options errorabend nofmterr;
/*******************************************************************************/
/*
/* Program: R:\05_Users\Norma\HALT-C\table_2_3_4.sas
/* Author:  Norma Pugh
/* Date:    February 2012
/* Purpose: Replicate select primary outcome results (Tables 2, 3 & 4).
/*
/*******************************************************************************/
/* DATA SOURCE */
libname data
'\\rcdubuntu01.rtp.rti.org\niddk\03_Data_And_Tools\Studies\HALT_C\Official_Archive\v3.0\HALT-C
Data\Analysis dataset\Publication_datasets';

/**************************/
/* DEFINE ANALYSIS DATASET */
/**************************/
data table_2_3_4; set data.Dienstag_2011_chc; run;
```

```
/*****************************/
/* REPLICATE ANALYSIS RESULTS */
/*****************************/
/* Annualized Incidence of SELECT Clinical Outcome, by Stratum */
title'Annualized Incidence of SELECT Clinical Outcome, by Stratum';
%macro life(years,evntyn,strata);
 proc lifetest data=table_2_3_4 intervals=1,2,3,4,5,6,7;
  time &years * &evntyn(0);
  strata &strata;
 run;
%mend life;

/* Table 2 */
%life(vh_life_year_a,vh_a,cirrhosis);
%life(ctp_vh_yrs,vh_a,ctp_a);
%life(asc_life_year_a,asc_a,cirrhosis);
%life(ctp_asc_yrs,asc_a,ctp_a);
%life(dth_life_yeara_a,dth_a,cirrhosis);
%life(ctp_dth_yrs,dth_a,ctp_a);
%life(liverdeath_trans_year,liverdeath_trans,cirrhosis);
%life(ctp_ldthtrans_yrs,liverdeath_trans,ctp_a);

/* Table 3 */
%life(vh_life_year_a,vh_a,female);
%life(vh_life_year_a,vh_a,age50);
%life(asc_life_year_a,asc_a,female);
%life(asc_life_year_a,asc_a,age50);
%life(dth_life_yeara_a,dth_a,female);
%life(dth_life_yeara_a,dth_a,age50);
%life(liverdeath_trans_year,liverdeath_trans,female);
%life(liverdeath_trans_year,liverdeath_trans,age50);

/* Table 4 */
%life(vh_life_year_a,vh_a,pltcate_a);
%life(asc_life_year_a,asc_a,pltcate_a);
%life(dth_life_yeara_a,dth_a,pltcate_a);
%life(liverdeath_trans_year,liverdeath_trans,pltcate_a);
```