Dataset Integrity Check for SyNCH (SyNCH: Silymarin in NASH and C Hepatitis)

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Revision History

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1 Standard Disclaimer

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, etc. Experience suggests that most discrepancies can ordinarily be resolved by consultation with the study data coordinating center (DCC), however this process is labor-intensive for both DCC and Repository staff. It is thus not our policy to resolve every discrepancy that is 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 Study Background[1]

Chronic hepatitis C viral (HCV) infections can cause a variety of serious consequences. These include cirrhosis, liver failure, and liver cancer. A large proportion of p-patients with HCV do not favorably to current therapies (peginterferon and ribavirin frequently combined with a protease inhibitor). There is thus a need for alternative or supplementary treatments for patients who do not respond favorably to current therapies.

Silymarin (Silybum marianum – an extract of milk thistle) has been used as a botanical treatment for HCV. Approximately 33% of HCV patients report current or past use of Silymarin. Prior clinical studies of efficacy of Silymarin have yielded inconsistent results, and they have been compromised by a variety of methodological flaws.

To provide better evidence on the efficacy of Silymarin as a therapy for HCV, the SyNCH study group conducted a randomized clinical trial with primary support from NIH's National Center for Complementary and Alternative Medicine (NCCAM) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK. Subjects were "adult patients with chronic HCV infection were eligible for the trial if they had received previous IFN-based therapy without sustained virological response, had quantifiable serum HCV RNA levels, and had an alanine aminotransferase (ALT) level of 65 U/L or greater at screening (1)." Patients were ineligible for the trial if there was evidence of demopensated hepatic cirrhosis, HIV, or one of several other conditions. Patients were also excluded from the trial if they had "a positive result for HBsAg (surface antigen of the hepatitis B virus), or had used milk thistle products within the previous 30 days. Liver biopsy was not required for entry, although if obtained, the presence of moderate steatosis or steatohepatitis were considered exclusions." (1)

One hundred and fifty four patients who met the eligibility criteria for the SyNCH clinical trial were randomly assigned to one of three treatment groups: (1) Placebo, (2) a 420mg dose of Silymarin administered three times a day, or (3) a 700mg dose of Silymarin administered three times a day. The treatment was continued for 24 weeks.

The primary outcome measure for the clinical trial was attaining a: "serum ALT level of 45 U/L or less (approximate normal range) or attainment of at least 50% decline of serum ALT level to less than 65 U/L

[1] Description derived from (Fried et al, 2012).

(approximately 1.5 times the upper limit of normal) after the 24-week treatment period."(1) The authors note that this primary outcome measure was chosen because it is: "a practical measure that has been correlated with improvement in hepatic necroinflammatory activity during studies of interferon for HCV infection."(1)

Study measurements were made baseline (week 0) and weeks 2, 4, 6, 8, 12, 16, 20, and 24. Measurements in week 6 and 16 were made in a telephone interview. Additional follow-up measurements were made 4 and 12 week after the conclusion of the clinical trial.

3 Archived Datasets

Sixteen SAS datasets[2] were retrieved from the Central Repository's archive. For analysis, these datasets were converted to Stata format using Stat/Transfer version 11 (Circle Systems).

4 Statistical Methods

The DCC did not create an "analysis file" for preparation of their 2012 JAMA article. It was thus necessary to extract required data elements from 16 individual datasets that encoded the randomization, demographic, laboratory, psychological scale, adverse event, and other data. This was a tedious and potentially error-prone process of creating multiple merged datasets for analysis. This process was hampered by complications such as the existence of multiple re-screenings of the same patient prior to trail admission, and missing outcome laboratory measurements at 24 weeks which required substitution of prior measurements.

Three primary merged datasets were created for use in this DSIC analysis: (1) for replication of Table1 a merge of datasets SE, LEV, RF, CD, and QD, (2) for replication of Table 2, a merge of data from AE and treatment randomization from RF, and (3) for replication of Table 3, a flat file containing one record for each trial participant ID, treatment group and ALT measurements for all time periods (so that the measurement closest to week 24 could be used if week 24 was missing).

[2] ad.sas7bdat, aev.sas7bdat cd.sas7bdat, dc.sas7bdat ds.sas7bdat, hcvrna_results.sas7bdat, lev.sas7bdat, ml.sas7bdat, op.sas7bdat, pd.sas7bdat, qd.sas7bdat, ql.sas7bdat, rf.sas7bdat, sc.sas7bdat, se.sas7bdat, ve.sas7bdat.

This DSIC analysis attempted to replicate the frequency counts, medians, and inter-quartile ranges reported in Table 1, 3, and the primary end points reported in Table 2. We do not replicate results using the SF-36 form because it appears to use a copyrighted scoring algorithm that is unavailable to us.

Analysis Strategy. Our analysis sought to replicate: (1) numerical results in published Table 1, (2) the primary trial outcomes reported in published Table 2, and (3) the results for "all adverse events" reported in published Table 3 of the Target SyNCH publication by Fried et al. (1).

To replicate published Table 1, we:

- generated numeric ID numbers for each of the datasets used in this replication to enable dataset merging;
- generated unduplicated screening data (SE and LEV) – both interview and lab data – for required measurements by eliminating (multiple) re-screenings and retaining only the most recent (re-) screening measurements;
- generated analyses for selected Table 1 variables (shown in normal typeface in Table 1) from the (most recent) screening data;
- generated Table 1 lab analysis for variables (shown in bold type) by using the baseline lab measurement, if available, or the most recent (re-) screening measurement if baseline measurement was unavailable; and
- calculated Table 1 scores for depression (CES-D) and chronic liver symptoms (CLDQ) scales.

To replicate the primary outcome measures reported in published Table 2, we:

- sequentially extracted lab measurements for each study time period (e.g., screening, baseline, week 2, ... week 24) and merged the resultant datasets to produce a flat file containing lab values for every time period, e.g., fasting glucose at screening, time 0, 2, ... 24; albumin at screening, time 0, 2, ... 24; etc.
- created an ALT outcome variable that contained measurements at week 24 – or the most recent time period available; and
- using this ALT measurement and a parallel measurement for baseline ALT (or the ALT screening measurement closest o Baseline) replicated analyses reported for primary outcomes in published Table 2.

To replicate the analysis of total adverse outcome measures reported in published Table 3, we:

- extracted the indicator of randomized treatment condition from the RF file;
- merged these data with adverse event reporting data – dropping subjects who reported no adverse events; and
- ran analyses to replicate results reported in Table 3 for persons reporting any adverse events.

5 Results

Tables 1 to 3 present the results of this analysis. With a single exception (Fasting Glucose at Baseline in Placebo condition), our results provide an exact or very close match to published results from Tables 1 to 3 of Fried et al.

6 Conclusions

These results provide excellent evidence that the SyNCH datasets deposited at the NIDDK Central Repository are accurate copies of the study's data.

7 References

1. Fried MW, Navarro VJ, Afdhal N, Belle SH, Wahed AS, Hawke RL, Doo E, Meyers CM, Reddy KR; Silymarin in NASH and C Hepatitis (SyNCH) Study Group. Effect of silymarin (milk thistle) on liver disease in patients with chronic hepatitis C unsuccessfully treated with interferon therapy: a randomized controlled trial. JAMA. 2012, 308(3):274-82.
2. 2. Hays RD, Sherbourne CD, Mazel RM. The RAND 36-item health survey 1.0, Health Economics, 1993, 2(3): 217–227.

8 Tables

Table 1. Baseline characteristics of Study Participants: Published vs. Results calculated using data archived in NIDDK Central Data Repository.

			Silymarin		
CHARACTERISTICS (a)	**Source**	**All**	**Placebo**	**420 mg**	**700 mg**
Sampe Size, (N)	Published	*(N = 154)*	*(n = 52)*	*(n = 50)*	*(n = 52)*
	Calculated	*(N = 154)*	*(n = 52)*	*(n = 50)*	*(n = 52)*
Age, median (IQR, y	Published	54.0 (51.0-58.0)	56.0 (51.5-59.5)	54.0 (52.0-57.0)	54.0 (48.0-58.0)
	Calculated	54.4 (50.4-58.0)	56.3 (51.3-59.0)	53.8 (51.3-56.7)	54.2 (48.1-58.1)
Men, No. (%)	Published	110 (71.4)	41 (78.9)	34 (68.0)	35 (67.3)
	Calculated	110 (71.4)	41 (78.9)	34 (68.0)	35 (67.3)
Race/ethnicity, No. (%) [(b)]					
White	Published	114 (75.0)	45 (88.2)	36 (72.0)	33 (64.7)
	Calculated	116 (75.3)	46 (88.5)	37 (74.0)	33 (63.5)
Black	Published	31 (20.4)	5 (9.8)	11 (22.0)	15 (29.4)
	Calculated	33 (21.4)	6 (11.5)	12 (24.0)	15 (28.9)

			Silymarin		
CHARACTERISTICS (a)	**Source**	**All**	**Placebo**	**420 mg**	**700 mg**
Other	Published	7 (4.6)	1 (2.0)	3 (6.0)	3 (5.9)
	Calculated	6 (3.9)	1 (1.9)	2 (4.0)	3 (5.8)
Hispanic	Published	8 (5.2)	3 (5.8)	3 (6.0)	2 (3.9)
	Calculated	8 (5.2)	3 (5.8)	3 (6.0)	2 (3.9)
BMI (IQR)	Published	29.2 (26.5-32.7)	29.1 (25.6-32.7)e	28.5 (26.0-32.4)	30.2 (28.1-32.9)
	Calculated	29.2 (26.5-32.7)	29.1 (25.6-32.7)	28.5 (26.0-32.4)	30.2 (28.1-32.9)
History of diabetes, No. (%)	Published	21 (13.6)	8 (15.4)	6 (12.0)	7 (13.5)
	Calculated	21 (13.6)	8 (15.4)	6 (12.0)	7 (13.5)
History of any milk thistle prep. use, No. (%)	Published	68	24 (46.2)	22 (44.0)	22 (42.3)
	Calculated	68 (44.2)	24 (46.2)	22 (44.0)	22 (42.3)
HCV genotype, No. (%)					
1	Published	139 (91.5)	44 (88.0)	47 (94.0)	48 (92.3)
	Calculated	139 (91.5)	44 (88.0)	47 (94.0)	48 (92.3)

			Silymarin		
CHARACTERISTICS (a)	**Source**	**All**	**Placebo**	**420 mg**	**700 mg**
2, 3, or 4	Published	13 (8.5)	6 (12.0)	3 (6.0)	4 (7.7)
	Calculated	13 (8.6)	6 (12.0)	3 (6.0)	4 (7.7)
HCV RNA, median (IQR), log10 IU/L	Published	6.2 (5.8-6.6)	6.4 (5.9-6.7)	6.1 (5.7-6.5)	6.3 (5.8-6.6)
	Calculated	6.2 (5-8-6.6)	6.4 (5.9-6.7)	6.1 (5.7-6.5)	6.3 (5.8-6.6)
Albumin, median (IQR), g/dL	Published	4.2 (3.9-4.4)	4.3 (3.9-4.5)e	4.1 (3.9-4.4)	4.1 (4.0-4.4)
	Calculated	4.2 (3.9-4.4)	4.3 (3.9-4.5)	4.1 (3.9-4.4)	4.1 (4.0-4.4)
ALT, median (IQR), U/L	Published	107.0 (83.0-150.0)	106.0 (83.0-136.0)	109.5 (83.0-158.0)	104.5 (83.5-151.0)
	Calculated	107 (83-150)	106 (83-136)	109.5 (83-158)	104.5 (83.5-151)
Creatinine, median (IQR), mg/dL	Published	0.8 (0.7-1.0)	0.9 (0.7-1.0)	0.8 (0.7-1.0)	0.8 (0.8-1.0)
	Calculated	0.8 (0.7-1.0)	0.9 (0.7-1.0)	0.8 (0.7-1.0)	0.8 (0.8-1.0)
Fasting glucose, median (IQR), mg/dL	Published	93.0 (83.0-105.0)	91.5 (80.0-106.0)g	93.0 (83.0-103.0)h	93.0 (83.0-113.0)
	Calculated	94 (83-106)	94.5 (83-106.5)	93 (83-103)	93.5 (83-110)

			Silymarin		
CHARACTERISTICS (a)	**Source**	**All**	**Placebo**	**420 mg**	**700 mg**
Hemoglobin, median (IQR), g/dL	Published	15.0 (14.2-15.8)	15.2 (14.2-15.9)	15.0 (14.1-15.6)	15.0 (14.2-15.9)
	Calculated	15.0 (14.2-15.8)	15.2 (14.2-15.9)	15.0 (14.1-15.6)	15.0 (14.2-15.9)
Platelets, median (IQR), x103 cells/µL	Published	177.0 (133.0-217.0)	180.0 (138.5-228.0)	173.0 (132.0-227.0)	177.0 (134.0-206.5)
	Calculated	177 (133-217)	180 (138.5-228)	173 (132-227)	177 (134-206.5)
Total bilirubin, median (IQR), mg/dL	Published	0.8 (0.6-1.0)	0.9 (0.6-1.1)	0.8 (0.6-1.0)	0.8 (0.6-1.0)
	Calculated	0.8 (0.6-1.0)	0.85 (0.55-1.1)	0.8 (0.6-1.0)	0.8 (0.6-1.0)
White blood cells, median (IQR), cells/µL	Published	5700 (4700-6900)	5800 (4900-6900)	5500 (4600-6500)	5600 (4900-7100)
	Calculated	5700 (4700-6900)	5750 (4850-6900)	5500 (4600-6500)	5600 (4900-7100)
CLDQ score, median (IQR)i	Published	5.8 (5.1-6.3)	5.8 (5.1-6.3)	6.0 (5.4-6.4)e	5.7 (4.8-6.3)
	Calculated	5.8 (5.2-6.3)	5.8 (5.2-6.3)	6.0 (5.4-6.4)	5.7 (4.8-6.3)
CES-D score, median (IQR)i	Published	8.0 (3.0-14.0)	7.5 (3.0-14.0)	8 (3-13.7)	8.5 (5.0-16.0)
	Calculated	8 (3-14)	7 (3-14)	8 (3-13)	(8 (5-16)

NOTE. We do not replicate results using the SF-36 form because it uses a copyrighted scoring algorithm that is unavailable to us.

Abbreviations: ALT = alanine aminotransferase; CES-D = Center for Epidemiologic Studies–Depression Scale; CLDQ = Chronic Liver Disease Questionnaire; HCV = hepatitis C virus; IQR = interquartile range.

(a) The published table indicates that data were missing for between 2 and 12 participants on the above measurements. Our calculations confirm the presence of a small amount of missing data although -- for reasons explained in the text -- the number of missing cases may not always match.

(b) The published table indicates that data on race/ethnicity were missing for 2 study participants. The DSIC analysis used the variables: racew, raceb, racea racei, raceh, and raceo which had 0-1 values for 154 study participants indicating whether they were white, black, Asian, American Indian, Hawaiian, or other. It was possible for a subject to be coded 1 for more than one category, e.g., white and black, white and Asian, etc.

Table 2. Analysis of Primary Outcome Measures.

		Silymarin		
		Placebo	**420 mg**	**700 mg**
Characteristics	**Source**	*(n = 52)*	*(n = 50)*	*(n = 52)*
PRIMARY OUTCOME 1: ALT of 45 or less N (%)				
	Published	1 (1.9)	2 (4.0)	1 (3.8)
	Calculated	1 (1.9)	2 (4.0)	1 (3.8)
PRIMARY OUTCOME 2: At least 50% ALT decline from baseline to week 24 and ALT < 65				
	Published	2 (3.8)	1 (2.0)	2 (3.8)
	Calculated	2 (3.9)	1 (2.0)	2 (3.9)
Either PRIMARY OUTCOME 1 or 2				
	Published	2 (3.8)	2 (4.0)	2 (3.8)
	Calculated	2 (3.9)	2 (4.0)	2 (3.9)

Table 3. Analysis of Number of Adverse Events and Serious Adverse Events by Treatment Group.

		Silymarin		
Characteristics*	**Source**	**Placebo**	**420 mg**	**700 mg**
All adverse events	Published	34	31	29
	Calculated	34	31	29
Serious adverse events	Published	1	6	5
	Calculated	1	6	5
Most common classes of adverse events				
Gastrointestinal	Published	4	8	6
	Calculated	4	8	6
Musculoskeletal	Published	4	2	3
	Calculated	4	2	3
Dermatologic	Published	3	0	4
	Calculated	3	0	4
Infection	Published	3	1	3
	Calculated	3	1	3
Physical injury	Published	1	1	3
	Calculated	1	1	3
Other	Published	19	19	10
	Calculated	19	19	10

***NOTE**. This comparison included data for all subjects reporting at one adverse event.

9 Appendix

The appendix is attached.