Dataset Integrity Check for the Nonalcoholic Steatohepatitis (NASH) Treatment of Nonalcoholic Fatty Liver Disease in Children (TONIC) Analysis Files

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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 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

Non-alcoholic fatty liver disease (NAFLD) is a clinicopathological diagnosis in which more than 5% of hepatocytes demonstrate macrovesicular steatosis in an individual without significant history of alcohol intake. NAFLD has become the most common cause of chronic liver disease in children in the United States, and encompasses a range of severity from bland steatosis to nonalcoholic steatohepatitis (NASH) that may ultimately result in advanced fibrosis, cirrhosis, and hepatocellular carcinoma. NAFLD was selected as the histologic entry criterion for this study because of a lack of knowledge about the natural history in the pediatric subset.

Treatment approaches to NAFLD in adults and children target reduction in insulin resistance and oxidative stress. Based on pediatric pilot data demonstrating potential efficacy of metformin or vitamin E, the NASH Clinical Research Network (NASH CRN), initiated a phase 3, multicenter, randomized, double-blinded, placebo-controlled trial evaluating vitamin E or metformin for the Treatment of NAFLD in Children (TONIC). The purpose of this study was to determine if therapeutic modification of insulin resistance or oxidative stress leads to improvement in serum or histologic indicators of liver injury or quality of life.

173 eligible patients were randomized in permuted blocks of treatments stratified by clinical center. Patients were assigned in a 1:1:1 ratio to 1 of 3 groups for 96 weeks of treatment, either (1) oral metformin (500 mg twice daily) and vitamin E placebo twice daily, (2) vitamin E (400 IU twice daily) and metformin placebo twice daily, or (3) vitamin E placebo and metformin placebo, each twice daily.

3 Archived Datasets

All SAS data files, as provided by the Data Coordinating Center (DCC), are located in the NASH "Analysis_Files" folder in the data package. For this replication, variables were taken from "table1", "table 2", "table 3", and "table 4" datasets. These datasets are analysis datasets created by the DCC .

4 Statistical Methods

Analyses were performed to duplicate results for the data published by Lavine et al [1] JAMA, April 27, 2011—Vol 305, No. 16.

To verify the integrity of the four dataset, descriptive statistics of baseline characteristics were computed, by treatment group (Table B, table D, table E, and table G).

5 Results

Table 1 in the publication [1], Baseline Characteristics by Treatment Group. Table A lists the variables that were used in the replication and Table B compares the results calculated from the archived data file to the results published in Table 1. The results of the replication are similar to the published results, within rounding error.

Table 2 in the publication [1] Primary Outcome: Sustained Reduction in ALT lever by treatment group. Table C lists the variables that were used in the replication and Table D compares the results calculated from the archived data file to the results published in Table 2. The results of the replication are the same as published results.

Table 3 in the publication [1] Changes from Baseline to End of Treatment in Liver Histology by Treatment Group. Table E lists the variables that were used in the replication and Table F compares the results calculated from the archived data file to the results published in Table 3. The results of the replication are similar to the published results, within rounding error.

Table 4 in the publication [1] Changes From Baseline to End of Treatment in Serum Biochemical Test Results, Metabolic Characteristics, and Quality of Life by Treatment Group. Table G lists the variables we used in our replication and Table H compares the results calculated from the archived data file to the results published in Table 4. The results of the replication are similar to the published results, within rounding error.

6 Conclusions

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

7References

Joel E. Lavine, Jeffrey B. Schwimmer, Mark L. Van Natta, Jean P. Molleston, Karen F. Murray, Philip Rosenthal, Stephanie H. Abrams, Ann O. Scheimann, Arun J. Sanyal, Naga Chalasani, James Tonascia, AynurU¨ nalp, Jeanne M. Clark, Elizabeth M. Brunt, David E. Kleiner, Jay H. Hoofnagle, Patricia R. Robuck; for the NASH CRN. Effect of Vitamin E or Metformin for Treatment of Nonalcoholic Fatty Liver Disease in Children and Adolescents The TONIC Randomized Controlled Trial. *JAMA, April 27, 2011—Vol 305, No. 16*

Table A: Variables used to replicate Table 1: Baseline Characteristics by Treatment Group

Table Variable	Variables Used in Replication from the "Table 1" Dataset
Age	AGE
Female	FEMALE
Hispanic ethnicity	HISPANIC
Race	RACE
Self-reported QOL score: Physical health	HLTH
Self-reported QOL score: Psychosocial health	PSYCH
Parent/guardian-reported QOL score: Physical health	PHLTH
Parent/guardian-reported QOL score: Psychosocial health	PPSYCH
AST, U/L	AST
ALT, U/L	ALT
GGT, U/L	GGT
Alkaline phosphatase, U/L	ALKA
Total bilirubin, mg/dL	BILIT
a.-Tocopherol, mg/L	VITE
Triglycerides, mg/dL	TRIG
Total cholesterol, mg/dL	CHOL
HDL, mg/dL	HDL
LDL, mg/dL	LDL
HOMA-IR, mg/dL x ?U/mL/405	HOMA
Fasting serum glucose, mg/dL	GLUC
Weight, kg	WEIGHT
Waist circumference, cm	WAIST
BMIc	BMI
BMI z score	BMIZ
Body composition, % total fatd	TOTALF
Tanner stagee	TANNER
Fibrosis stage	BLFIBRO
Definite NASH, No. (%)	DEFNASH
Steatosis score	BLSTEATO
Lobular inflammation score	BLINFLAM
Ballooning degeneration score	BLBALL
NAFLD activity score	BLNAS

Table B: Comparison of values computed in integrity check to reference article Table 1 values

characteristic	Vitamin E (n=58) Mean (SD) [Manuscript]	Vitamin E (n=58) Mean (SD) [DSIC]	Vitamin E (n=58) Mean (SD) [Difference]
Age, y	13.4 (2.3)	13.4 (2.3)	0.0 (0.0)
Female sex, No. (%)	11 (19.0)	11.0 (19.0)	0.0 (0.0)
Hispanic ethnicity, No. (%)	36 (62.1)	36.0 (62.1)	0.0 (0.0)
RACE: American Indian or Alaska Native	7 (12.1)	7.0 (12.1)	0.0 (0.0)
RACE: Asian	1 (1.7)	1.0 (1.7)	0.0 (0.0)
RACE: Black or African American	3 (5.2)	3.0 (5.2)	0.0 (0.0)
RACE: Native Hawaiian or other Pacific Islander	0.0(0.0)	0.0 (0.0)	0.0 (0.0)
RACE: White	40 (69.0)	40.0 (69.0)	0.0 (0.0)
RACE: >=2 Races	1 (1.7)	1.0 (1.7)	0.0 (0.0)
RACE: Refusal/not stated	6 (10.3)	6.0 (10.3)	0.0 (0.0)
Self-reported QOL score: Physical health	78 (17)	78 (17)	0 (0)
Self-reported QOL score: Psychosocial health	70 (19)	70 (19)	0 (0)
Parent/guardian-reported QOL score: Physical health"	66 (23)	66 (23)	0 (0)
Parent/guardian-reported QOL score: Psychosocial health	64 (18)	64 (18)	0 (0)
AST, U/L	70 (37)	70 (37)	0 (0)
ALT, U/L	121 (65)	121 (65)	0 (0)
GGT, U/L	50 (25)	50 (25)	0 (0)
Alkaline phosphatase, U/L	220 (94)	220 (94)	0 (0)
Total bilirubin, mg/dL	0.68 (0.33)	0.68 (0.33)	0.00 (0.00)
a.-Tocopherol, mg/L	9.5 (4.9)	9.5 (4.9)	0.0 (0.0)
Triglycerides, mg/dL	154 (107)	154 (107)	0 (0)
Total cholesterol, mg/dL	179 (42)	179 (42)	0 (0)
HDL, mg/dL	37 (9)	37 (9)	0 (0)
LDL, mg/dL	114 (34)	114 (34)	0 (0)
HOMA-IR, mg/dL x U/mL/405	8.6 (7.8)	8.6 (7.8)	0.0 (0.0)
Fasting serum glucose, mg/dL	87 (8)	87 (8)	0 (0)
Weight, kg	91 (28)	91 (28)	0 (0)
Waist circumference, cm	108 (18)	109 (16)	-1 (2)
BMIc	34 (7)	34 (7)	0 (0)

characteristic	Vitamin E (n=58) Mean (SD) [Manuscript]	Vitamin E (n=58) Mean (SD) [DSIC]	Vitamin E (n=58) Mean (SD) [Difference]
BMI z score	2.33 (0.34)	2.27 (0.40)	0.06 (-0.06)
Body composition, % total fat	44 (6)	44 (6)	0 (0)
Tanner stagee	2.6 (1.5)	2.6 (1.5)	0.0 (0.0)
Fibrosis stage	1.2 (1.0)	1.2 (1.0)	0.0 (0.0)
Definite NASH, No. (%)	27 (46.6)	27.0 (46.6)	0.0 (0.0)
Steatosis score	2.3 (0.8)	2.3 (0.8)	0.0 (0.0)
Lobular inflammation score	1.6 (0.6)	1.6 (0.6)	0.0 (0.0)
Ballooning degeneration score	1.0 (0.8)	1.0 (0.8)	0.0 (0.0)
NAFLD activity score	4.8 (1.6)	4.8 (1.6)	0.0 (0.0)

characteristic	Metformin (n=57) Mean (SD) [Manuscript]	Metformin (n=57) Mean (SD) [DSIC]	Metformin (n=57) Mean (SD) [Difference]
Age, y	13.1 (2.4)	13.1 (2.4)	0.0 (0.0)
Female sex, No. (%)	10 (17.5)	10.0 (17.5)	0.0 (0.0)
Hispanic ethnicity, No. (%)	31 (54.4)	31.0 (54.4)	0.0 (0.0)
RACE: American Indian or Alaska Native	6 (10.5)	6.0 (10.5)	0.0 (0.0)
RACE: Asian	2 (3.5)	2.0 (3.5)	0.0 (0.0)
RACE: Black or African American	1 (1.8)	1.0 (1.8)	0.0 (0.0)
RACE: Native Hawaiian or other Pacific Islander	0	0.0 (0.0)	0.0 (0.0)
RACE: White	43 (75.4)	43.0 (75.4)	0.0 (0.0)
RACE: >=2 Races	1 (1.8)	1.0 (1.8)	0.0 (0.0)
RACE: Refusal/not stated	4 (7.0)	4.0 (7.0)	0.0 (0.0)
Self-reported QOL score: Physical health	77 (18)	77 (18)	0 (0)
Self-reported QOL score: Psychosocial health	71 (16)	71 (16)	0 (0)
Parent/guardian-reported QOL score: Physical health"	64 (23)	64 (23)	0 (0)
Parent/guardian-reported QOL score: Psychosocial health	62 (19)	62 (19)	0 (0)
AST, U/L	69 (45)	69 (45)	0 (0)
ALT, U/L	121 (68)	121 (68)	0 (0)
GGT, U/L	52 (51)	52 (51)	0 (0)
Alkaline phosphatase, U/L	237 (99)	237 (99)	0 (0)
Total bilirubin, mg/dL	0.64 (0.25)	0.64 (0.25)	0.00 (0.00)
a.-Tocopherol, mg/L	8.4 (2.7)	8.4 (2.7)	0.0 (0.0)
Triglycerides, mg/dL	151 (103)	151 (103)	0 (0)
Total cholesterol, mg/dL	174 (45)	174 (45)	0 (0)
HDL, mg/dL	38 (7)	38 (7)	0 (0)
LDL, mg/dL	105 (30)	105 (30)	0 (0)
HOMA-IR, mg/dL x U/mL/405	7.9 (5.4)	7.9 (5.4)	0.0 (0.0)
Fasting serum glucose, mg/dL	90 (10)	90 (10)	0 (0)
Weight, kg	88 (23)	88 (23)	0 (0)
Waist circumference, cm	104 (13)	108 (13)	-4 (0)
BMIc	34 (5)	34 (5)	0 (0)

characteristic	Metformin (n=57) Mean (SD) [Manuscript]	Metformin (n=57) Mean (SD) [DSIC]	Metformin (n=57) Mean (SD) [Difference]
BMI z score	2.35 (0.30)	2.29 (0.35)	0.06 (-0.05)
Body composition, % total fat	44 (7)	44 (7)	0 (0)
Tanner stagee	2.6 (1.4)	2.6 (1.4)	0.0 (0.0)
Fibrosis stage	1.3 (1.0)	1.3 (1.0)	0.0 (0.0)
Definite NASH, No. (%)	24 (42.1)	24.0 (42.1)	0.0 (0.0)
Steatosis score	2.1 (0.8)	2.1 (0.8)	0.0 (0.0)
Lobular inflammation score	1.6 (0.6)	1.6 (0.6)	0.0 (0.0)
Ballooning degeneration score	0.8 (0.8)	0.8 (0.8)	0.0 (0.0)
NAFLD activity score	4.5 (1.2)	4.5 (1.2)	0.0 (0.0)

characteristic	Placebo (n=58) Mean (SD) [Manuscript]	Placebo (n=58) Mean (SD) [DSIC]	Placebo (n=58) Mean (SD) [Difference]
Age, y	12.9 (2.6)	12.9 (2.6)	0.0 (0.0)
Female sex, No. (%)	12 (20.7)	12.0 (20.7)	0.0 (0.0)
Hispanic ethnicity, No. (%)	39 (67.2)	39.0 (67.2)	0.0 (0.0)
RACE: American Indian or Alaska Native	10 (17.2)	10.0 (17.2)	0.0 (0.0)
RACE: Asian	0	0.0 (0.0)	0.0 (0.0)
RACE: Black or African American	0	0.0 (0.0)	0.0 (0.0)
RACE: Native Hawaiian or other Pacific Islander	1 (1.7)	1.0 (1.7)	0.0 (0.0)
RACE: White	45 (77.6)	45.0 (77.6)	0.0 (0.0)
RACE: >=2 Races	0	0.0 (0.0)	0.0 (0.0)
RACE: Refusal/not stated	2 (3.4)	2.0 (3.5)	0.0 (-0.1)
Self-reported QOL score: Physical health	76 (21)	76 (21)	0 (0)
Self-reported QOL score: Psychosocial health	68 (19)	68 (19)	0 (0)
Parent/guardian-reported QOL score: Physical health"	65 (24)	65 (24)	0 (0)
Parent/guardian-reported QOL score: Psychosocial health	61 (21)	61 (21)	0 (0)
AST, U/L	74 (42)	74 (42)	0 (0)
ALT, U/L	126 (62)	126 (62)	0 (0)
GGT, U/L	50 (32)	50 (32)	0 (0)
Alkaline phosphatase, U/L	229 (93)	229 (93)	0 (0)
Total bilirubin, mg/dL	0.63 (0.32)	0.63 (0.32)	0.00 (0.00)
a.-Tocopherol, mg/L	9.3 (4.8)	9.3 (4.8)	0.0 (0.0)
Triglycerides, mg/dL	153 (92)	153 (92)	0 (0)
Total cholesterol, mg/dL	176 (35)	176 (35)	0 (0)
HDL, mg/dL	38 (10)	38 (10)	0 (0)
LDL, mg/dL	108 (27)	108 (27)	0 (0)
HOMA-IR, mg/dL x U/mL/405	11.0 (17.6)	11.0 (17.6)	0.0 (0.0)
Fasting serum glucose, mg/dL	90 (9)	90 (9)	0 (0)
Weight, kg	86 (24)	86 (24)	0 (0)
Waist circumference, cm	105 (12)	106 (14)	-1 (-2)
BMIc	33 (6)	33 (6)	0 (0)

characteristic	Placebo (n=58) Mean (SD) [Manuscript]	Placebo (n=58) Mean (SD) [DSIC]	Placebo (n=58) Mean (SD) [Difference]
BMI z score	2.35 (0.26)	2.28 (0.32)	0.07 (-0.06)
Body composition, % total fat	43 (7)	43 (7)	0 (0)
Tanner stagee	2.5 (1.5)	2.5 (1.5)	0.0 (0.0)
Fibrosis stage	1.2 (1.0)	1.2 (1.0)	0.0 (0.0)
Definite NASH, No. (%)	22 (37.9)	22.0 (37.9)	0.0 (0.0)
Steatosis score	2.1 (0.8)	2.1 (0.8)	0.0 (0.0)
Lobular inflammation score	1.7 (0.6)	1.7 (0.6)	0.0 (0.0)
Ballooning degeneration score	0.8 (0.8)	0.8 (0.8)	0.0 (0.0)
NAFLD activity score	4.6 (1.3)	4.6 (1.3)	0.0 (0.0)

Table C: Variables used to replicate Table 2: Primary Outcome: Sustained Reduction in ALT level by Treatment Group

Table Variable	**Variables Used in Replication from the "Table 2" Dataset**
Sustained reduction in ALT level	PRIMARY
Change in ALT level from baseline, Week 24	calt24
Change in ALT level from baseline, Week 48	calt48
Change in ALT level from baseline, Week 72	calt72
Change in ALT level from baseline, Week 96	calt96

Table D: Comparison of values computed in integrity check to reference article Table 2 values

characteristic	Vitamin E (n=58) N(%) or mean(95% CI) [Manuscript]	Vitamin E (n=58) N(%) or mean(95% CI) [DSIC]	Vitamin E (n=58) N(%) or mean(95% CI) [Difference]
Sustained reduction in ALT level	15 (26)	15 (26)	0 (0)
calt24	-49.2 (-64.4 to -33.9)	-49.2 (-64.8 to -33.6)	0.0 (0.4 to -0.3)
calt48	-44.5 (-60.3 to -28.7)	-44.5 (-60.7 to -28.3)	0.0 (0.4 to -0.4)
calt72	-44.2 (-65.9 to -22.5)	-44.2 (-66.5 to -22.0)	0.0 (0.6 to -0.5)
calt96	-48.3 (-66.8 to -29.8)	-48.3 (-67.3 to -29.4)	0.0 (0.5 to -0.4)

characteristic	Metformin (n=57) N(%) or mean(95% CI) [Manuscript]	Metformin (n=57) N(%) or mean(95% CI) [DSIC]	Metformin (n=57) N(%) or mean(95% CI) [Difference]
Sustained reduction in ALT level	9 (16)	9 (16)	0 (0)
calt24	-3.0 (-21.1 to 15.0)	-3.0 (-21.6 to 15.5)	0.0 (0.5 to -0.5)
calt48	-11.7 (-45.3 to 22.0)	-11.7 (-46.2 to 22.9)	0.0 (0.9 to -0.9)
calt72	-20.5 (-59.8 to 18.8)	-20.5 (-60.9 to 19.9)	0.0 (1.1 to -1.1)
calt96	-41.7 (-62.9 to -20.5)	-41.7 (-63.4 to -19.9)	0.0 (0.5 to -0.6)

characteristic	Placebo (n=58) N(%) or mean(95% CI) [Manuscript]	Placebo (n=58) N(%) or mean(95% CI) [DSIC]	Placebo (n=58) N(%) or mean(95% CI) [Difference]
Sustained reduction in ALT level	10 (17)	10 (17)	0 (0)
calt24	-24.5 (-43.0 to -5.9)	-24.5 (-43.5 to -5.4)	0.0 (0.5 to -0.5)
calt48	-25.0 (-43.7 to -6.4)	-25.0 (-44.2 to -5.9)	0.0 (0.5 to -0.5)
calt72	-36.4 (-57.1 to -15.8)	-36.4 (-57.7 to -15.2)	0.0 (0.6 to -0.6)
calt96	-35.2 (-56.9 to -13.5)	-35.2 (-57.4 to -12.9)	0.0 (0.5 to -0.6)

Table E: Variables used to replicate Table 3: Changes From Baseline to End of Treatment in Liver Histology by Treatment Group

Table Variable	**Variables Used in Replication from the "Table 3" Dataset**
Fibrosis score improved	ifibro1
Fibrosis score change	dfibro
Steatosis score improved	isteato1
Steatosis score change	dsteato
Lobular inflammation score improved	iinflam1
Lobular inflammation score change	dinflam
Ballooning degeneration score improved	iball1
Ballooning degeneration score change	dball
Change in NAFLD activity score	dnas
Resolution of NASH	resolve

Table F: Comparison of values computed in integrity check to reference article Table 3 values

characteristic	Vitamin E (n=50) N(%) or mean(95% CI) [Manuscript]	Vitamin E (n=50) N(%) or mean(95% CI) [DSIC]	Vitamin E (n=50) N(%) or mean(95% CI) [Difference]
ifibro1	18 (37)	18 (37)	0 (0)
dfibro	-0.3 (-0.6 to 0.0)	-0.3 (-0.6 to 0.0)	0.0 (0.0 to 0.0)
isteato1	27 (54)	27 (54)	0 (0)
dsteato	-0.8 (-1.1 to -0.5)	-0.8 (-1.1 to -0.5)	0.0 (0.0 to 0.0)
iinflam1	22 (44)	22 (44)	0 (0)
dinflam	-0.4 (-0.6 to -0.2)	-0.4 (-0.6 to -0.2)	0.0 (0.0 to 0.0)
iball1	22 (44)	22 (44)	0 (0)
dball	-0.5 (-0.8 to -0.3)	-0.5 (-0.8 to -0.3)	0.0 (0.0 to 0.0)
dnas	-1.8 (-2.4 to -1.2)	-1.8 (-2.4 to -1.2)	0.0 (0.0 to 0.0)
resolve	25 (58)	25 (58)	0 (0)

characteristic	Metformin (n=50) N(%) or mean(95% CI) [Manuscript]	Metformin (n=50) N(%) or mean(95% CI) [DSIC]	Metformin (n=50) N(%) or mean(95% CI) [Difference]
ifibro1	22 (44)	22 (44)	0 (0)
dfibro	-0.4 (-0.7 to -0.0)	-0.4 (-0.7 to -0.0)	0.0 (0.0 to 0.0)
isteato1	26 (52)	26 (52)	0 (0)
dsteato	-0.6 (-0.9 to -0.2)	-0.6 (-0.9 to -0.2)	0.0 (0.0 to 0.0)
iinflam1	23 (46)	23 (46)	0 (0)
dinflam	-0.3 (-0.5 to -0.0)	-0.3 (-0.5 to 0.0)	0.0 (0.0 to 0.0)
iball1	22 (44)	22 (44)	0 (0)
dball	-0.3 (-0.6 to -0.0)	-0.3 (-0.6 to 0.0)	0.0 (0.0 to 0.0)
dnas	-1.1 (-1.7 to -0.5)	-1.1 (-1.8 to -0.5)	0.0 (0.1 to 0.0)
resolve	16 (41)	16 (41)	0 (0)

characteristic	Placebo (n=47) N(%) or mean(95% CI) [Manuscript]	Placebo (n=47) N(%) or mean(95% CI) [DSIC]	Placebo (n=47) N(%) or mean(95% CI) [Difference]
ifibro1	19 (40)	19 (40)	0 (0)
dfibro	-0.2 (-0.6 to 0.1)	-0.2 (-0.6 to 0.1)	0.0 (0.0 to 0.0)
isteato1	19 (40)	19 (40)	0 (0)
dsteato	-0.4 (-0.8 to -0.1)	-0.5 (-0.8 to -0.1)	0.1 (0.0 to 0.0)
iinflam1	20 (43)	20 (43)	0 (0)
dinflam	-0.3 (-0.6 to -0.1)	-0.3 (-0.6 to -0.1)	0.0 (0.0 to 0.0)
iball1	10 (21)	10 (21)	0 (0)
dball	0.1 (-0.2 to 0.3)	0.1 (-0.2 to 0.3)	0.0 (0.0 to 0.0)
dnas	-0.7 (-1.3 to -0.2)	-0.7 (-1.3 to -0.2)	0.0 (0.0 to 0.0)
resolve	11 (28)	11 (28)	0 (0)

Table G: Variables used to replicate Table 4: Changes from Baseline to End of Treatment in Serum Biochemistry Test Results, Lipid Level, Metabolic Characteristics, and Quality of Life by Treatment Group

Table Variable	Variables Used in Replication from the "Table 4" Dataset
Change in self-reported QOL: Physical health	CHLTH
Change in self-reported QOL: Psychosocial health	CPSYCH
Change in parent/guardian-reported QO: Physical health	CPHLTH
Change in parent/guardian-reported QOP: psychosocial health	CPPSYCH
ALT, U/L	CALT
AST, U/L	CAST
GGT, U/L	CGGT
Alkaline phosphatase, U/L	CALKA
Total bilirubin, mg/dL	CBILIT
a.-Tocopherol, mg/L	CVITE
Triglycerides, mg/dL	CTRIG
Total cholesterol, mg/dL	CCHOL
HDL, mg/dL	CHDL
LDL, mg/dL	CLDL
HOMA-IR, mg/dL x ?U/mL/405	CHOMA
Fasting serum glucose, mg/dL	CGLUC
Weight, kg	CWEIGHT
Waist circumference, cm	CWAIST
BMIc	CBMI
BMI z score	CBMIZ
Body composition, % total fatd	CTOTALF
Tanner stage	CTANNER

Table H: Comparison of values computed in integrity check to reference article Table 4 values

characteristic	Vitamin E (n=50) mean(95% CI) [Manuscript]	Vitamin E (n=50) mean(95% CI) [DSIC]	Vitamin E (n=50) mean(95% CI) [Difference]
CHLTH	7.6 (2.7 to 12.5)	7.6 (2.6 to 12.6)	0.0 (0.1 to -0.1)
CPSYCH	6.0 (1.4 to 10.6)	6.0 (1.3 to 10.7)	0.0 (0.1 to -0.1)
CPHLTH	1.5 (-7.9 to 11.0)	1.5 (-8.2 to 11.2)	0.0 (0.3 to -0.2)
CPPSYCH	4.3 (-1.6 to 10.1)	4.3 (-1.8 to 10.3)	0.0 (0.2 to -0.2)
CALT	-48.3 (-66.8 to -29.8)	-48.3 (-67.3 to -29.4)	0.0 (0.5 to -0.4)
CAST	-22.8 (-33.3 to -12.3)	-22.8 (-33.6 to -12.0)	0.0 (0.3 to -0.3)
CGGT	-7.4 (-33.3 to -12.3)	-7.4 (-13.5 to -1.4)	0.0 (-19.8 to -10.9)
CALKA	-49.2 (-68.5 to -29.9)	-49.2 (-69.0 to -29.4)	0.0 (0.5 to -0.5)
CBILIT	0.05 (-0.05 to 0.15)	0.05 (-0.06 to 0.16)	0.00 (0.01 to -0.01)
CVITE	9.4 (6.2 to 12.6)	9.4 (6.1 to 12.7)	0.0 (0.1 to -0.1)
CTRIG	35.2 (9.8 to 60.6)	35.2 (9.2 to 61.3)	0.0 (0.6 to -0.7)
CCHOL	-2.5 (-10.6 to 5.7)	-2.5 (-10.8 to 5.9)	0.0 (0.2 to -0.2)
CHDL	-3.7 (-5.3 to -2.2)	-3.7 (-5.3 to -2.2)	0.0 (0.0 to 0.0)
CLDL	-5.2 (-13.0 to 2.6)	-5.2 (-13.2 to 2.8)	0.0 (0.2 to -0.2)
CHOMA	0.6 (-2.7 to 3.9)	0.6 (-2.8 to 4.0)	0.0 (0.1 to -0.1)
CGLUC	1.1 (-2.6 to 4.7)	1.1 (-2.7 to 4.8)	0.0 (0.1 to -0.1)
CWEIGHT	13.3 (10.2 to 16.4)	13.3 (10.1 to 16.5)	0.0 (0.1 to -0.1)
CWAIST	5.7 (3.5 to 7.9)	5.7 (3.4 to 7.9)	0.0 (0.1 to 0.0)
CBMI	2.1 (1.2 to 3.0)	2.1 (1.1 to 3.0)	0.0 (0.1 to 0.0)
CBMIZ	-0.03 (-0.11 to 0.06)	-0.03 (-0.12 to 0.06)	0.00 (0.01 to 0.00)
CTOTALF	-1.1 (-2.6 to 0.4)	-1.1 (-2.6 to 0.4)	0.0 (0.0 to 0.0)
CTANNER	1.3 (1.0 to 1.6)	1.3 (1.0 to 1.6)	0.0 (0.0 to 0.0)

characteristic	Metformin (n=51) mean(95% CI) [Manuscript]	Metformin (n=51) mean(95% CI) [DSIC]	Metformin (n=51 mean(95% CI)) [Difference]
CHLTH	5.4 (0.8 to 10.0)	5.4 (0.7 to 10.1)	0.0 (0.1 to -0.1)
CPSYCH	4.0 (-0.4 to 8.4)	4.0 (-0.5 to 8.5)	0.0 (0.1 to -0.1)
CPHLTH	4.1 (-3.8 to 12.0)	4.1 (-4.0 to 12.2)	0.0 (0.2 to -0.2)
CPPSYCH	1.9 (-4.0 to 7.8)	1.9 (-4.2 to 7.9)	0.0 (0.2 to -0.1)
CALT	-41.7 (-62.9 to -20.5)	-41.7 (-63.4 to -19.9)	0.0 (0.5 to -0.6)
CAST	-21.5 (-34.6 to -8.4)	-21.5 (-34.9 to -8.0)	0.0 (0.3 to -0.4)
CGGT	-14.3 (-24.9 to -3.7)	-14.3 (-25.2 to -3.5)	0.0 (0.3 to -0.2)
CALKA	-70.0 (-91.2 to -48.8)	-70.0 (-91.7 to -48.3)	0.0 (0.5 to -0.5)
CBILIT	0.03 (-0.05 to 0.10)	0.03 (-0.05 to 0.11)	0.00 (0.00 to -0.01)
CVITE	-0.5 (-1.1 to 0.2)	-0.5 (-1.2 to 0.2)	0.0 (0.1 to 0.0)
CTRIG	2.1 (-21.3 to 25.5)	2.1 (-21.9 to 26.1)	0.0 (0.6 to -0.6)
CCHOL	-6.7 (-14.7 to 1.3)	-6.7 (-14.9 to 1.5)	0.0 (0.2 to -0.2)
CHDL	-0.8 (-2.6 to 1.0)	-0.8 (-2.6 to 1.0)	0.0 (0.0 to 0.0)
CLDL	-6.1 (-11.9 to -0.3)	-6.1 (-12.1 to -0.2)	0.0 (0.2 to -0.1)
CHOMA	-0.0 (-1.9 to 1.8)	-0.0 (-1.9 to 1.9)	0.0 (0.0 to -0.1)
CGLUC	-1.0 (-4.3 to 2.2)	-1.0 (-4.4 to 2.3)	0.0 (0.1 to -0.1)
CWEIGHT	12.0 (9.3 to 14.6)	12.0 (9.3 to 14.7)	0.0 (0.0 to -0.1)
CWAIST	3.9 (1.7 to 6.2)	4.0 (1.6 to 6.3)	-0.1 (0.1 to -0.1)
CBMI	1.3 (0.6 to 2.0)	1.3 (0.6 to 2.0)	0.0 (0.0 to 0.0)
CBMIZ	-0.06 (-0.13 to 0.00)	-0.06 (-0.13 to 0.00)	0.00 (0.00 to 0.00)
CTOTALF	-2.4 (-3.6 to -1.2)	-2.4 (-3.7 to -1.2)	0.0 (0.1 to 0.0)
CTANNER	1.3 (1.0 to 1.7)	1.4 (1.0 to 1.7)	-0.1 (0.0 to 0.0)

characteristic	Placebo (n=49) mean(95% CI) [Manuscript]	Placebo (n=49) mean(95% CI) [DSIC]	Placebo (n=49) mean(95% CI) [Difference]
CHLTH	5.4 (-0.7 to 11.5)	5.4 (-0.9 to 11.7)	0.0 (0.2 to -0.2)
CPSYCH	5.6 (-0.0 to 11.2)	5.6 (-0.2 to 11.4)	0.0 (0.2 to -0.2)
CPHLTH	4.8 (-1.5 to 11.0)	4.8 (-1.6 to 11.1)	0.0 (0.1 to -0.1)
CPPSYCH	6.1 (0.1 to 12.2)	6.2 (-0.0 to 12.3)	-0.1 (0.1 to -0.1)
CALT	-35.2 (-56.9 to -13.5)	-35.2 (-57.4 to -12.9)	0.0 (0.5 to -0.6)
CAST	-20.4 (-32.7 to -8.0)	-20.4 (-33.0 to -7.7)	0.0 (0.3 to -0.3)
CGGT	-4.4 (-11.6 to 2.8)	-4.4 (-11.8 to 3.0)	0.0 (0.2 to -0.2)
CALKA	-50.2 (-66.7 to -33.6)	-50.2 (-67.2 to -33.2)	0.0 (0.5 to -0.4)
CBILIT	0.12 (0.04 to 0.20)	0.12 (0.04 to 0.20)	0.00 (0.00 to 0.00)
CVITE	-0.9 (-2.1 to 0.4)	-0.9 (-2.2 to 0.4)	0.0 (0.1 to 0.0)
CTRIG	18.9 (1.3 to 36.5)	18.9 (0.9 to 37.0)	0.0 (0.4 to -0.5)
CCHOL	-7.5 (-15.2 to 0.3)	-7.5 (-15.5 to 0.5)	0.0 (0.3 to -0.2)
CHDL	-2.6 (-4.6 to -0.6)	-2.6 (-4.7 to -0.5)	0.0 (0.1 to -0.1)
CLDL	-6.2 (-13.2 to 0.7)	-6.3 (-13.4 to 0.9)	0.1 (0.2 to -0.2)
CHOMA	-1.4 (-8.3 to 5.6)	-1.4 (-8.5 to 5.8)	0.0 (0.2 to -0.2)
CGLUC	4.2 (-2.7 to 11.2)	4.2 (-2.9 to 11.4)	0.0 (0.2 to -0.2)
CWEIGHT	12.7 (9.7 to 15.6)	12.7 (9.6 to 15.7)	0.0 (0.1 to -0.1)
CWAIST	5.6 (2.5 to 8.6)	5.6 (2.4 to 8.7)	0.0 (0.1 to -0.1)
CBMI	1.9 (1.1 to 2.7)	1.9 (1.0 to 2.8)	0.0 (0.1 to -0.1)
CBMIZ	-0.01 (-0.08 to 0.06)	-0.01 (-0.08 to 0.06)	0.00 (0.00 to 0.00)
CTOTALF	-1.9 (-3.5 to -0.3)	-1.9 (-3.6 to -0.3)	0.0 (0.1 to 0.0)
CTANNER	1.2 (1.0 to 1.5)	1.3 (0.9 to 1.6)	-0.1 (0.1 to -0.1)

Attachment A: SAS Code

```
/*************************************************************************************************
**********************
***Program: /prj/niddk/ims_analysis/NASH/prog_initial_analysis/nash_integrity_check.sas;
***Programmer: Jane Wang
***Date Created: 11/05/2013
***Purpose: To perform a Dataset Integrity Check (DSIC) between the  data and the primary outcome
paper:
***Joel E. Lavine, Jeffrey B. Schwimmer, Mark L. Van Natta, Jean P. Molleston, Karen F. Murray,
Philip Rosenthal,
***Stephanie H. Abrams, Ann O. Scheimann, Arun J. Sanyal, Naga Chalasani, James Tonascia, AynurU¨
nalp, Jeanne M. Clark,
***Elizabeth M. Brunt, David E. Kleiner, Jay H. Hoofnagle, Patricia R. Robuck; for the NASH CRN.
Effect of Vitamin E or
***Metformin for Treatment of Nonalcoholic Fatty Liver Disease in Children and Adolescents The
TONIC Randomized Controlled Trial
***        The numbers in Tables 1,2,3 and 4 of the primary outcome paper will compared to the
NASH data received;
*************************************************************************************************
**********************/;

title1 "%sysfunc(getoption(sysin))";
title2 " ";

options nofmterr;

*** Reading in the analysis datasets used for the DSIC;
libname inlib4 xport
"/prj/niddk/ims_analysis/NASH/private_orig_data/NASHCRN_Data_Sharing_TONIC_JAMA_2011/Datasets/tab
le4.xpt";
proc copy in =inlib4  out= work;
libname inlib5 xport
"/prj/niddk/ims_analysis/NASH/private_orig_data/NASHCRN_Data_Sharing_TONIC_JAMA_2011/Datasets/tab
le1.xpt";
proc copy in =inlib5  out= work;
libname inlib6 xport
"/prj/niddk/ims_analysis/NASH/private_orig_data/NASHCRN_Data_Sharing_TONIC_JAMA_2011/Datasets/tab
le2.xpt";
proc copy in =inlib6  out= work;
libname inlib7 xport
"/prj/niddk/ims_analysis/NASH/private_orig_data/NASHCRN_Data_Sharing_TONIC_JAMA_2011/Datasets/tab
le3.xpt";
proc copy in =inlib7  out= work;

*** Data from the Primary outcome paper that was converted to .csv format so that the DSIC data
could be easily compared;
FILENAME table1  '/prj/niddk/ims_analysis/NASH/private_created_data/nash_tonic_table1_data.csv';
FILENAME table2  '/prj/niddk/ims_analysis/NASH/private_created_data/nash_tonic_table2_data.csv';
FILENAME table3  '/prj/niddk/ims_analysis/NASH/private_created_data/nash_tonic_table3_data.csv';
FILENAME table4  '/prj/niddk/ims_analysis/NASH/private_created_data/nash_tonic_table4_data.csv';


*** Output CSV files that will be converted to .xls before being added to the DSIC document;
FILENAME out_t1
'/prj/niddk/ims_analysis/NASH/private_created_data/nash_tonic_Jama_table1_dsic.csv';
FILENAME out_t2
'/prj/niddk/ims_analysis/NASH/private_created_data/nash_tonic_Jama_table2_dsic.csv';
FILENAME out_t3
'/prj/niddk/ims_analysis/NASH/private_created_data/nash_tonic_Jama_table3_dsic.csv';
FILENAME out_t4
'/prj/niddk/ims_analysis/NASH/private_created_data/nash_tonic_Jama_table4_dsic.csv';

%macro baseline_freq(dataset_name,var_name);

       *** Creating a frequency table in the format of Table 1 in the primary outcome paper;
  proc freq data = &dataset_name;
       table (&var_name.)*TX;
       title3 "Frequency table of the &var_name. variable in the analysis dataset";
```

```
       *** Outputting the frequency data to work.&var_name._cross using the ODS output;
  ods output CrossTabFreqs = work.&var_name._cross;
   proc print data = &var_name._cross;
     title3 "&var_name._cross";

       *** Creating two datases (one per arm) so that the data can be in the correct format;
       data &var_name._cross_Placebo &var_name._cross_VitE &var_name._cross_Met
&var_name._cross_all;
         set &var_name._cross;
              if TX = "1Vit"  and not missing(&var_name. )  then do;first_stat =
round(Frequency,0.01); second_stat = round(colpercent,0.01); output &var_name._cross_VitE;    end;
         else if TX = "2Met"  and not missing(&var_name. )  then do;first_stat =
round(Frequency,0.01); second_stat = round(colpercent,0.01); output &var_name._cross_Met;     end;
         else if TX = "3Plb"  and not missing(&var_name. )  then do;first_stat =
round(Frequency,0.01); second_stat = round(colpercent,0.01); output &var_name._cross_Placebo; end;
         else if TX = ""      and not missing(&var_name. )  then do;first_stat =
round(Frequency,0.01); second_stat = round(Percent,0.01);    output &var_name._cross_all;     end;
    else if lengthn(TX) NE 0 and (not missing(&var_name. )) then abort;


*** Creating a dataset with the merged data with the variables that contain the order of the
statisitics;
       data &var_name._merge;
         merge &var_name._cross_Placebo (in = in1 keep= table &var_name. first_stat second_stat
rename = (first_stat = first_stat_Placebo second_stat  = second_stat_Placebo))
               &var_name._cross_VitE    (in = in2 keep= table &var_name. first_stat second_stat
rename = (first_stat = first_stat_VitE    second_stat  = second_stat_VitE   ))
               &var_name._cross_Met     (in = in3 keep= table &var_name. first_stat second_stat
rename = (first_stat = first_stat_Met     second_stat  = second_stat_Met    ))
               &var_name._cross_all     (in = in4 keep= table &var_name. first_stat second_stat
rename = (first_stat = first_stat_all     second_stat  = second_stat_all    ))
               ;
       by table &var_name.;
              if in1 and in2 and in3 and in4 then output &var_name._merge;
       else abort;

%mend;



%macro baseline_median(dataset_name,var_name);

  proc sort data = &dataset_name;
    by TX;

       *** Creating a means table in the format of Table 1 in the primary outcome paper that
contain the median 25th percentile and 75th percentile;
  proc means data = &dataset_name mean Std  ;
    var &var_name.;
    by TX;

       *** Outputting the statisitics to the work.&var_name._summary dataset using the ODS
output;
  ods output Summary = work.&var_name._means1;

  proc print data = &var_name._means1;
    title3 "&var_name._means1";

       *** Creating two datases (one per arm) so that the data can be in the correct format;
       data &var_name._means_Placebo &var_name._means_VitE &var_name._means_Met;
         set &var_name._means1;
    length table_name $ 30.;
         table_name =  upcase("&var_name.");
              if TX = "1Vit" then do; first_stat = round(&var_name._Mean,0.01); second_stat =
round(&var_name._StdDev,0.01);output &var_name._means_VitE;    end;
         else if TX = "2Met" then do; first_stat = round(&var_name._Mean,0.01); second_stat =
round(&var_name._StdDev,0.01);output &var_name._means_Met ;    end;
         else if TX = "3Plb" then do; first_stat = round(&var_name._Mean,0.01); second_stat =
round(&var_name._StdDev,0.01);output &var_name._means_Placebo; end;
```

```
  proc means data = &dataset_name mean Std  ;
    var &var_name.;

        *** Outputting the statisitics to the work.&var_name._summary dataset using the ODS
output;
  ods output Summary = work.&var_name._means_all;

  proc print data = &var_name._means_all;
    title3 "&var_name._means_all";

  data &var_name._means_all;
    set &var_name._means_all;
    length table_name $ 30.;
         table_name =  upcase("&var_name.");
    first_stat = round(&var_name._Mean,0.01);
    second_stat = round(&var_name._StdDev,0.01);

*** Creating a dataset with the merged data with the variables that contain the order of the
statisitics;
       data &var_name._means;
         merge
               &var_name._means_VitE    (in = in2 keep = table_name  first_stat second_stat
rename = (first_stat = first_stat_VitE    second_stat = second_stat_VitE   ))
               &var_name._means_Met     (in = in2 keep = table_name  first_stat second_stat
rename = (first_stat = first_stat_Met     second_stat = second_stat_Met    ))
               &var_name._means_Placebo (in = in1 keep = table_name  first_stat second_stat
rename = (first_stat = first_stat_Placebo second_stat = second_stat_Placebo))
               &var_name._means_all     (in = in2 keep = table_name  first_stat second_stat
rename = (first_stat = first_stat_all     second_stat = second_stat_all    ))
               ;
       by table_name;

  proc print data = &var_name._means;
    title3 "&var_name._means";

%mend;

%macro baseline_univariate(dataset_name,var_name);

  proc sort data = &dataset_name;
    by TX;

        *** Creating a means table in the format of Table 1 in the primary outcome paper that
contain the median 25th percentile and 75th percentile;
  proc univariate data = &dataset_name cibasic  ;
    var &var_name.;
    by TX;

        *** Outputting the statisitics to the work.&var_name._summary dataset using the ODS
output;
  ods output BasicIntervals = work.&var_name._uni;

*  proc print data = &var_name._uni;
*    title3 "&var_name._uni";

        *** Creating two datases (one per arm) so that the data can be in the correct format;
        data &var_name._uni_Placebo &var_name._uni_VitE &var_name._uni_Met;
          set &var_name._uni;
    length table_name $ 30.;
    if Parameter = 'Mean';
          table_name =  upcase("&var_name.");
               if TX = "1Vit" then do; first_stat = round(Estimate,0.01); second_stat =
round(LowerCL,0.01);third_stat = round(UpperCL,0.01);output &var_name._uni_VitE;    end;
          else if TX = "2Met" then do; first_stat = round(Estimate,0.01); second_stat =
round(LowerCL,0.01);third_stat = round(UpperCL,0.01);output &var_name._uni_Met ;    end;
          else if TX = "3Plb" then do; first_stat = round(Estimate,0.01); second_stat =
round(LowerCL,0.01);third_stat = round(UpperCL,0.01);output &var_name._uni_Placebo; end;

        data &var_name._univariate;
```

```
         merge &var_name._uni_Placebo (in = in1 keep = table_name  first_stat second_stat
third_stat rename = (first_stat = first_stat_Placebo second_stat = second_stat_Placebo third_stat
= third_stat_Placebo))
               &var_name._uni_VitE    (in = in2 keep = table_name  first_stat second_stat
third_stat rename = (first_stat = first_stat_VitE    second_stat = second_stat_VitE    third_stat
= third_stat_VitE   ))
               &var_name._uni_Met     (in = in2 keep = table_name  first_stat second_stat
third_stat rename = (first_stat = first_stat_Met     second_stat = second_stat_Met     third_stat
= third_stat_Met    ))
               ;
       by table_name;
*  proc print data = &var_name._univariate;
*    title3 "&var_name._univariate";

%mend;



*******************************************************************************;
*************** Check Table 1 *************************************************;
*******************************************************************************;

*** Running the baseline_freq on the  categorical variables in the Table 1 manuscript file;
%baseline_freq(table1,FEMALE     );
%baseline_freq(table1,hispanic   );
%baseline_freq(table1,race       );
%baseline_freq(table1,defnash   );

data compare_table1_freq(drop = table FEMALE hispanic race defnash);
  set FEMALE_merge                    (keep = table FEMALE   first_stat_Placebo first_stat_VitE
first_stat_Met first_stat_all second_stat_Placebo second_stat_VitE second_stat_Met
second_stat_all where = (FEMALE  = 0))
      hispanic_merge      (keep = table hispanic first_stat_Placebo first_stat_VitE
first_stat_Met first_stat_all second_stat_Placebo second_stat_VitE second_stat_Met
second_stat_all where = (hispanic = 1))
      race_merge          (keep = table race     first_stat_Placebo first_stat_VitE
first_stat_Met first_stat_all second_stat_Placebo second_stat_VitE second_stat_Met
second_stat_all where = (RACE ne ''))
      defnash_merge       (keep = table defnash  first_stat_Placebo first_stat_VitE
first_stat_Met first_stat_all second_stat_Placebo second_stat_VitE second_stat_Met
second_stat_all where = (defnash  = 1) )
;
  length table_name $ 30.;
  table_name = substr(table,7,length(table)-11);


data compare_table1_freq;
  set compare_table1_freq;
    if _n_ = 3       then table_name = 'RACE1';
    else if  _n_ = 4 then table_name = 'RACE2';
    else if  _n_ = 5 then table_name = 'RACE3';
    else if  _n_ = 6 then table_name = 'RACE4';
    else if  _n_ = 7 then table_name = 'RACE5';
    else if  _n_ = 8 then table_name = 'RACE6';
    else if  _n_ = 9 then table_name = 'RACE7';

proc print data = compare_table1_freq;
  title3 'compare_table1_freq';

*** Running the baseline_media on the  continuous variables in the Table 1 manuscript file;

%baseline_median(table1,age        );
%baseline_median(table1,HLTH       );
%baseline_median(table1,PSYCH      );
%baseline_median(table1,PHLTH      );
%baseline_median(table1,PPSYCH     );
%baseline_median(table1,AST        );
%baseline_median(table1,ALT        );
%baseline_median(table1,GGT        );
%baseline_median(table1,ALKA       );
%baseline_median(table1,BILIT      );
```

```
%baseline_median(table1,VITE       );
%baseline_median(table1,TRIG       );
%baseline_median(table1,CHOL       );
%baseline_median(table1,HDL        );
%baseline_median(table1,LDL        );
%baseline_median(table1,HOMA       );
%baseline_median(table1,GLUC       );
%baseline_median(table1,WEIGHT     );
%baseline_median(table1,WAIST      );
%baseline_median(table1,BMI        );
%baseline_median(table1,BMIZ       );
%baseline_median(table1,TOTALF     );
%baseline_median(table1,TANNER     );
%baseline_median(table1,BLFIBRO    );
%baseline_median(table1,BLSTEATO   );
%baseline_median(table1,BLINFLAM   );
%baseline_median(table1,BLBALL     );
%baseline_median(table1,BLNAS      );


data compare_table1_mean;
  set
age_means
HLTH_means
PSYCH_means
PHLTH_means
PPSYCH_means
AST_means
ALT_means
GGT_means
ALKA_means
BILIT_means
VITE_means
TRIG_means
CHOL_means
HDL_means
LDL_means
HOMA_means
GLUC_means
WEIGHT_means
WAIST_means
BMI_means
BMIZ_means
TOTALF_means
TANNER_means
BLFIBRO_means
BLSTEATO_means
BLINFLAM_means
BLBALL_means
BLNAS_means
  ;
data compare_table1;
  set compare_table1_freq compare_table1_mean;
  length char_compare_stat1-char_compare_stat4 $ 30.;
  if table_name in ('BILIT' 'BMIZ') then do;
          char_compare_stat1 = strip(put(first_stat_VitE   ,8.2))  || " ( " ||
strip(put(second_stat_VitE   ,8.2)) || " ) ";
          char_compare_stat2 = strip(put(first_stat_Met    ,8.2))  || " ( " ||
strip(put(second_stat_Met    ,8.2)) || " ) ";
          char_compare_stat3 = strip(put(first_stat_Placebo,8.2))  || " ( " ||
strip(put(second_stat_Placebo,8.2)) || " ) ";
          char_compare_stat4 = strip(put(first_stat_all    ,8.2))  || " ( " ||
strip(put(second_stat_all    ,8.2)) || " ) ";
  end;
  else if table_name in ('AGE' 'FEMALE' 'HISPANIC' 'RACE1' 'RACE2' 'RACE3' 'RACE4' 'RACE5'
'RACE6' 'RACE7' 'VITE' 'HOMA' 'TANNER'
                         'BLFIBRO' 'DEFNASH' 'BLSTEATO' 'BLINFLAM' 'BLBALL' 'BLNAS') then do;
          char_compare_stat1 = strip(put(first_stat_VitE   ,8.1))  || " ( " ||
strip(put(second_stat_VitE   ,8.1)) || " ) ";
          char_compare_stat2 = strip(put(first_stat_Met    ,8.1))  || " ( " ||
strip(put(second_stat_Met    ,8.1)) || " ) ";
```

```
         char_compare_stat3 = strip(put(first_stat_Placebo,8.1))  || " ( " ||
strip(put(second_stat_Placebo,8.1)) || " ) ";
         char_compare_stat4 = strip(put(first_stat_all    ,8.1))  || " ( " ||
strip(put(second_stat_all    ,8.1)) || " ) ";
  end;
  else if table_name in ('HLTH' 'PSYCH' 'PHLTH' 'PPSYCH' 'AST' 'ALT' 'GGT' 'ALKA' 'TRIG'
                         'CHOL' 'HDL' 'LDL' 'GLUC' 'WEIGHT' 'WAIST' 'BMI' 'TOTALF') then do;
         char_compare_stat1 = strip(put(first_stat_VitE   ,8.))  || " ( " ||
strip(put(second_stat_VitE   ,8.)) || " ) ";
         char_compare_stat2 = strip(put(first_stat_Met    ,8.))  || " ( " ||
strip(put(second_stat_Met    ,8.)) || " ) ";
         char_compare_stat3 = strip(put(first_stat_Placebo,8.))  || " ( " ||
strip(put(second_stat_Placebo,8.)) || " ) ";
         char_compare_stat4 = strip(put(first_stat_all    ,8.))  || " ( " ||
strip(put(second_stat_all    ,8.)) || " ) ";
  end;


*proc print data = compare_table1;
*  title3 'compare_table1';

*** Importing the Table 1 Data taken from the primary outcome paper;
data table1_data;
  infile table1 delimiter = ',' MISSOVER DSD  firstobs=3 ls=1080;
  length characteristic $45 table_name $30 char_stat1-char_stat4 $23 ;
  input
  characteristic $ table_name $ stat1 stat2   stat3   stat4   stat5   stat6   stat7   stat8
char_stat1 $   char_stat2 $   char_stat3 $   char_stat4     $
;
  if lengthn(characteristic) NE 0 then output table1_data;

data table1_data;
  set table1_data;
  sort_order = _n_;
  table_name = upcase(table_name);

*** Merging the DSIC Table 1 data and the Table 1 data from the manuscript;
*** Creating variables to calculate the difference between the datasets;
proc sort data = compare_table1;
  by  table_name  ;
proc sort data = table1_data;
  by  table_name  ;

data combined_table1_dataset;
  merge compare_table1 (in = in1)
        table1_data     (in = in2)
        ;
  by table_name  ;
  if in1 and in2 then output combined_table1_dataset;

data combined_table1_dataset;
  set combined_table1_dataset;
  length char_diff1-char_diff4 $ 30.;

  if table_name in ('BILIT' 'BMIZ') then do;
      diff5   = round((round(stat5,0.01)   -  round(first_stat_Placebo ,0.01)),0.01);
      diff6   = round((round(stat6,0.01)   -  round(second_stat_Placebo,0.01)),0.01);
      diff1   = round((round(stat1,0.01)   -  round(first_stat_VitE    ,0.01)),0.01);
      diff2   = round((round(stat2,0.01)   -  round(second_stat_VitE   ,0.01)),0.01);
      diff3   = round((round(stat3,0.01)   -  round(first_stat_Met     ,0.01)),0.01);
      diff4   = round((round(stat4,0.01)   -  round(second_stat_Met    ,0.01)),0.01);
      diff7   = round((round(stat7,0.01)   -  round(first_stat_all     ,0.01)),0.01);
      diff8   = round((round(stat8,0.01)   -  round(second_stat_all    ,0.01)),0.01);

           char_diff1 = strip(put(diff1,8.2))  || " ( " || strip(put(diff2,8.2)) || " ) ";
           char_diff2 = strip(put(diff3,8.2))  || " ( " || strip(put(diff4,8.2)) || " ) ";
           char_diff3 = strip(put(diff5,8.2))  || " ( " || strip(put(diff6,8.2)) || " ) ";
           char_diff4 = strip(put(diff7,8.2))  || " ( " || strip(put(diff8,8.2)) || " ) ";
  end;
  else if table_name in ('AGE' 'FEMALE' 'HISPANIC' 'RACE1' 'RACE2' 'RACE3' 'RACE4' 'RACE5'
'RACE6' 'RACE7' 'VITE' 'HOMA' 'TANNER'
```

```
                        'BLFIBRO' 'DEFNASH' 'BLSTEATO' 'BLINFLAM' 'BLBALL' 'BLNAS') then do;
     diff5   = round((round(stat5,0.1)   -  round(first_stat_Placebo ,0.1)),0.1);
     diff6   = round((round(stat6,0.1)   -  round(second_stat_Placebo,0.1)),0.1);
     diff1   = round((round(stat1,0.1)   -  round(first_stat_VitE    ,0.1)),0.1);
     diff2   = round((round(stat2,0.1)   -  round(second_stat_VitE   ,0.1)),0.1);
     diff3   = round((round(stat3,0.1)   -  round(first_stat_Met     ,0.1)),0.1);
     diff4   = round((round(stat4,0.1)   -  round(second_stat_Met    ,0.1)),0.1);
     diff7   = round((round(stat7,0.1)   -  round(first_stat_all     ,0.1)),0.1);
     diff8   = round((round(stat8,0.1)   -  round(second_stat_all    ,0.1)),0.1);
          char_diff1  = strip(put(diff1,8.1))  || " ( " || strip(put(diff2,8.1)) || " ) ";
          char_diff2  = strip(put(diff3,8.1))  || " ( " || strip(put(diff4,8.1)) || " ) ";
          char_diff3  = strip(put(diff5,8.1))  || " ( " || strip(put(diff6,8.1)) || " ) ";
          char_diff4  = strip(put(diff7,8.1))  || " ( " || strip(put(diff8,8.1)) || " ) ";
  end;
  else if table_name in ('HLTH' 'PSYCH' 'PHLTH' 'PPSYCH' 'AST' 'ALT' 'GGT' 'ALKA' 'TRIG'
                        'CHOL' 'HDL' 'LDL' 'GLUC' 'WEIGHT' 'WAIST' 'BMI' 'TOTALF') then do;
     diff5   = round((round(stat5,1)   -  round(first_stat_Placebo ,1)),1);
     diff6   = round((round(stat6,1)   -  round(second_stat_Placebo,1)),1);
     diff1   = round((round(stat1,1)   -  round(first_stat_VitE    ,1)),1);
     diff2   = round((round(stat2,1)   -  round(second_stat_VitE   ,1)),1);
     diff3   = round((round(stat3,1)   -  round(first_stat_Met     ,1)),1);
     diff4   = round((round(stat4,1)   -  round(second_stat_Met    ,1)),1);
     diff7   = round((round(stat7,1)   -  round(first_stat_all     ,1)),1);
     diff8   = round((round(stat8,1)   -  round(second_stat_all    ,1)),1);
          char_diff1  = strip(put(diff1,8.))  || " ( " || strip(put(diff2,8.)) || " ) ";
          char_diff2  = strip(put(diff3,8.))  || " ( " || strip(put(diff4,8.)) || " ) ";
          char_diff3  = strip(put(diff5,8.))  || " ( " || strip(put(diff6,8.)) || " ) ";
          char_diff4  = strip(put(diff7,8.))  || " ( " || strip(put(diff8,8.)) || " ) ";
  end;
  label
     char_stat1         = "Vitamin E (n=58) Mean (SD) [Manuscript]"
     char_compare_stat1 = "Vitamin E (n=58) Mean (SD) [DSIC]      "
     char_diff1         = "Vitamin E (n=58) Mean (SD) [Difference]"
     char_stat2         = "Metfomin (n=57) Mean (SD) [Manuscript]"
     char_compare_stat2 = "Metfomin (n=57) Mean (SD) [DSIC]      "
     char_diff2         = "Metfomin (n=57) Mean (SD) [Difference]"
     char_stat3         = "Placebo (n=58) Mean (SD) [Manuscript]"
     char_compare_stat3 = "Placebo (n=58) Mean (SD) [DSIC]      "
     char_diff3         = "Placebo (n=58) Mean (SD) [Difference]"
  ;


*proc print data = combined_table1_dataset(keep =table_name char_diff1-char_diff4  char_stat1-
char_stat4 char_compare_stat1-char_compare_stat4);
*  title3 'combined_table1_dataset';
*proc freq data = combined_table1_dataset;
*  tables diff1-diff8/list missing;




*******************************************************************************;
************** Check Table 2 ***********************************************;
*******************************************************************************;

*** Running the baseline_freq on the  categorical variables in the Table 1 manuscript file;
%baseline_freq(table2,PRIMARY     );
data compare_table2_freq(drop = table PRIMARY);
  set PRIMARY_merge                   (keep = table PRIMARY   first_stat_Placebo first_stat_VitE
first_stat_Met  second_stat_Placebo second_stat_VitE second_stat_Met  where = (PRIMARY  = 1))
;
  length table_name $ 30.;
  table_name = substr(table,7,length(table)-11);

*proc print data = compare_table2_freq;
*  title3 'compare_table2_freq';


*** Running the baseline_media on the  continuous variables in the Table 2 manuscript file;

%baseline_univariate(table2,calt24      );
```

```
%baseline_univariate(table2,calt48      );
%baseline_univariate(table2,calt72      );
%baseline_univariate(table2,calt96      );

data compare_table2_uni;
  set calt24_univariate
      calt48_univariate
      calt72_univariate
      calt96_univariate
      ;

data compare_table2;
  set compare_table2_freq compare_table2_uni;
  length char_compare_stat1-char_compare_stat3 $ 30.;
  if table_name in ('PRIMARY') then do;
         char_compare_stat1 = strip(put(first_stat_VitE   ,8.))  || " ( "  ||
strip(put(second_stat_VitE   ,8.))  ||  " ) ";
         char_compare_stat2 = strip(put(first_stat_Met    ,8.))  || " ( "  ||
strip(put(second_stat_Met    ,8.))  ||  " ) ";
         char_compare_stat3 = strip(put(first_stat_Placebo,8.))  || " ( "  ||
strip(put(second_stat_Placebo,8.))  ||  " ) ";
  end;
  else do;
         char_compare_stat1 = strip(put(first_stat_VitE   ,8.1))  || " ( " ||
strip(put(second_stat_VitE   ,8.1)) || " to "  || strip(put(third_stat_VitE   ,8.1)) ||" ) ";
         char_compare_stat2 = strip(put(first_stat_Met    ,8.1))  || " ( " ||
strip(put(second_stat_Met    ,8.1)) || " to "  || strip(put(third_stat_Met    ,8.1)) ||" ) ";
         char_compare_stat3 = strip(put(first_stat_Placebo,8.1))  || " ( " ||
strip(put(second_stat_Placebo,8.1)) || " to "  || strip(put(third_stat_Placebo,8.1)) ||" ) ";
  end;

*proc print data = compare_table2;
*  title3 'compare_table2';

*** Importing the Table 2 Data taken from the primary outcome paper;
data table2_data;
  infile table2 delimiter = ',' MISSOVER DSD  firstobs=3 ls=1080;
  length characteristic $45 table_name $30 char_stat1-char_stat3 $23 ;
  input
  characteristic $ table_name $ stat1 stat2   stat3   stat4   stat5   stat6   stat7   stat8 stat9
char_stat1 $   char_stat2 $   char_stat3 $
;
  if lengthn(characteristic) NE 0 then output table2_data;

data table2_data;
  set table2_data;
  sort_order = _n_;
  table_name = upcase(table_name);

*** Merging the DSIC Table 2 data and the Table 2 data from the manuscript;
*** Creating variables to calculate the difference between the datasets;
proc sort data = compare_table2;
  by  table_name  ;
proc sort data = table2_data;
  by  table_name  ;

data combined_table2_dataset;
  merge compare_table2 (in = in1)
        table2_data     (in = in2)
        ;
  by table_name  ;
  if in1 and in2 then output combined_table2_dataset;

data combined_table2_dataset;
  set combined_table2_dataset;
  length char_diff1-char_diff3 $ 30.;

  if table_name in ('PRIMARY') then do;
     diff1   = round((round(stat1,1)   -  round(first_stat_VitE    ,1)),1);
     diff2   = round((round(stat2,1)   -  round(second_stat_VitE   ,1)),1);
     diff3   = round((round(stat4,1)   -  round(first_stat_Met     ,1)),1);
```

```
    diff4   = round((round(stat5,1)   -  round(second_stat_Met    ,1)),1);
    diff5   = round((round(stat7,1)   -  round(first_stat_Placebo ,1)),1);
    diff6   = round((round(stat8,1)   -  round(second_stat_Placebo,1)),1);
        char_diff1  = strip(put(diff1,8.))  || " ( " || strip(put(diff2,8.)) || " ) ";
        char_diff2  = strip(put(diff3,8.))  || " ( " || strip(put(diff4,8.)) || " ) ";
        char_diff3  = strip(put(diff5,8.))  || " ( " || strip(put(diff6,8.)) || " ) ";
  end;
  else do;
      diff1   = round((round(stat1,0.1)   -  round(first_stat_VitE    ,0.1)),0.1);
      diff2   = round((round(stat2,0.1)   -  round(second_stat_VitE   ,0.1)),0.1);
      diff3   = round((round(stat3,0.1)   -  round(third_stat_VitE    ,0.1)),0.1);
      diff4   = round((round(stat4,0.1)   -  round(first_stat_Met     ,0.1)),0.1);
      diff5   = round((round(stat5,0.1)   -  round(second_stat_Met    ,0.1)),0.1);
      diff6   = round((round(stat6,0.1)   -  round(third_stat_Met     ,0.1)),0.1);
      diff7   = round((round(stat7,0.1)   -  round(first_stat_Placebo ,0.1)),0.1);
      diff8   = round((round(stat8,0.1)   -  round(second_stat_Placebo,0.1)),0.1);
      diff9   = round((round(stat9,0.1)   -  round(third_stat_Placebo, 0.1)),0.1);
          char_diff1  = strip(put(diff1,8.1))  || " ( " || strip(put(diff2,8.1)) || " to " ||
strip(put(diff3,8.1)) || " ) ";
          char_diff2  = strip(put(diff4,8.1))  || " ( " || strip(put(diff5,8.1)) || " to " ||
strip(put(diff6,8.1)) || " ) ";
          char_diff3  = strip(put(diff7,8.1))  || " ( " || strip(put(diff8,8.1)) || " to " ||
strip(put(diff9,8.1)) || " ) ";
  end;
  label
     char_stat1         = "Vitamin E (n=58) N(%) or mean(95% CI) [Manuscript]"
     char_compare_stat1 = "Vitamin E (n=58) N(%) or mean(95% CI) [DSIC]      "
     char_diff1         = "Vitamin E (n=58) N(%) or mean(95% CI) [Difference]"
     char_stat2         = "Metfomin (n=57) N(%) or mean(95% CI) [Manuscript]"
     char_compare_stat2 = "Metfomin (n=57) N(%) or mean(95% CI) [DSIC]      "
     char_diff2         = "Metfomin (n=57) N(%) or mean(95% CI) [Difference]"
     char_stat3         = "Placebo (n=58) N(%) or mean(95% CI) [Manuscript]"
     char_compare_stat3 = "Placebo (n=58) N(%) or mean(95% CI) [DSIC]      "
     char_diff3         = "Placebo (n=58) N(%) or mean(95% CI) [Difference]"
  ;

*proc print data = combined_table2_dataset(keep =table_name char_diff1-char_diff3  char_stat1-
char_stat3 char_compare_stat1-char_compare_stat3);
*  title3 'combined_table2_dataset';
*proc freq data = combined_table2_dataset;
*  tables diff1-diff9/list missing;



*******************************************************************************;
*************** Check Table 3 ************************************************;
*******************************************************************************;
data table3;
  set table3;
  if INAS1 ne .;

%baseline_freq(table3,ifibro1      );
%baseline_freq(table3,isteato1      );
%baseline_freq(table3,iinflam1      );
%baseline_freq(table3,iball1      );
%baseline_freq(table3,resolve      );

data compare_table3_freq(drop = table ifibro1 isteato1 iinflam1 iball1 resolve );
  set ifibro1_merge                  (keep = table ifibro1   first_stat_Placebo first_stat_VitE
first_stat_Met  second_stat_Placebo second_stat_VitE second_stat_Met  where = (ifibro1   = 1))
      isteato1_merge                 (keep = table isteato1  first_stat_Placebo first_stat_VitE
first_stat_Met  second_stat_Placebo second_stat_VitE second_stat_Met  where = (isteato1  = 1))
      iinflam1_merge                 (keep = table iinflam1  first_stat_Placebo first_stat_VitE
first_stat_Met  second_stat_Placebo second_stat_VitE second_stat_Met  where = (iinflam1  = 1))
      iball1_merge                     (keep = table iball1    first_stat_Placebo
first_stat_VitE first_stat_Met  second_stat_Placebo second_stat_VitE second_stat_Met  where =
(iball1    = 1))
      resolve_merge                  (keep = table resolve   first_stat_Placebo first_stat_VitE
first_stat_Met  second_stat_Placebo second_stat_VitE second_stat_Met  where = (resolve   = 1))
;
  length table_name $ 30.;
```

```
  table_name = substr(table,7,length(table)-11);

*proc print data = compare_table3_freq;
*  title3 'compare_table3_freq';

%baseline_univariate(table3,dfibro      );
%baseline_univariate(table3,dsteato      );
%baseline_univariate(table3,dinflam      );
%baseline_univariate(table3,dball      );
%baseline_univariate(table3,dnas      );

data compare_table3_uni;
  set dfibro_univariate
      dsteato_univariate
      dinflam_univariate
      dball_univariate
      dnas_univariate   ;

*proc print data = compare_table3_uni;
*  title3 'compare_table3_uni';

data compare_table3;
  set compare_table3_freq compare_table3_uni;
  length char_compare_stat1-char_compare_stat3 $ 30.;
  if table_name in ('IFIBRO1' 'ISTEATO1' 'IINFLAM1' 'IBALL1' 'RESOLVE') then do;
         char_compare_stat1 = strip(put(first_stat_VitE   ,8.))  || " ( "  ||
strip(put(second_stat_VitE   ,8.))  ||  " ) ";
         char_compare_stat2 = strip(put(first_stat_Met    ,8.))  || " ( "  ||
strip(put(second_stat_Met    ,8.))  ||  " ) ";
         char_compare_stat3 = strip(put(first_stat_Placebo,8.))  || " ( "  ||
strip(put(second_stat_Placebo,8.))  ||  " ) ";
  end;
  else do;
         char_compare_stat1 = strip(put(first_stat_VitE   ,8.1))  || " ( " ||
strip(put(second_stat_VitE   ,8.1)) || " to "  || strip(put(third_stat_VitE   ,8.1)) ||" ) ";
         char_compare_stat2 = strip(put(first_stat_Met    ,8.1))  || " ( " ||
strip(put(second_stat_Met    ,8.1)) || " to "  || strip(put(third_stat_Met    ,8.1)) ||" ) ";
         char_compare_stat3 = strip(put(first_stat_Placebo,8.1))  || " ( " ||
strip(put(second_stat_Placebo,8.1)) || " to "  || strip(put(third_stat_Placebo,8.1)) ||" ) ";
  end;

*proc print data = compare_table3;
*  title3 'compare_table3';

*** Importing the Table 2 Data taken from the primary outcome paper;
data table3_data;
  infile table3 delimiter = ',' MISSOVER DSD  firstobs=2 ls=1080;
  length characteristic $45 table_name $30 char_stat1-char_stat3 $23 ;
  input
  characteristic $ table_name $ stat1 stat2   stat3   stat4   stat5   stat6   stat7   stat8 stat9
char_stat1 $   char_stat2 $   char_stat3 $
;
  if lengthn(characteristic) NE 0 then output table3_data;

data table3_data;
  set table3_data;
  sort_order = _n_;
  table_name = upcase(table_name);

*** Merging the DSIC Table 3 data and the Table 3 data from the manuscript;
*** Creating variables to calculate the difference between the datasets;
proc sort data = compare_table3;
  by  table_name  ;
proc sort data = table3_data;
  by  table_name  ;

data combined_table3_dataset;
  merge compare_table3 (in = in1)
        table3_data     (in = in2)
        ;
  by table_name  ;
```

```
  if in1 and in2 then output combined_table3_dataset;

data combined_table3_dataset;
  set combined_table3_dataset;
  length char_diff1-char_diff3 $ 30.;

  if table_name in ('IFIBRO1' 'ISTEATO1' 'IINFLAM1' 'IBALL1' 'RESOLVE') then do;
     diff1   = round((round(stat1,1)   -  round(first_stat_VitE    ,1)),1);
     diff2   = round((round(stat2,1)   -  round(second_stat_VitE   ,1)),1);
     diff3   = round((round(stat4,1)   -  round(first_stat_Met     ,1)),1);
     diff4   = round((round(stat5,1)   -  round(second_stat_Met    ,1)),1);
     diff5   = round((round(stat7,1)   -  round(first_stat_Placebo ,1)),1);
     diff6   = round((round(stat8,1)   -  round(second_stat_Placebo,1)),1);
         char_diff1  = strip(put(diff1,8.))  || " ( " || strip(put(diff2,8.)) || " ) ";
         char_diff2  = strip(put(diff3,8.))  || " ( " || strip(put(diff4,8.)) || " ) ";
         char_diff3  = strip(put(diff5,8.))  || " ( " || strip(put(diff6,8.)) || " ) ";
  end;
  else do;
      diff1   = round((round(stat1,0.1)   -  round(first_stat_VitE    ,0.1)),0.1);
      diff2   = round((round(stat2,0.1)   -  round(second_stat_VitE   ,0.1)),0.1);
      diff3   = round((round(stat3,0.1)   -  round(third_stat_VitE    ,0.1)),0.1);
      diff4   = round((round(stat4,0.1)   -  round(first_stat_Met     ,0.1)),0.1);
      diff5   = round((round(stat5,0.1)   -  round(second_stat_Met    ,0.1)),0.1);
      diff6   = round((round(stat6,0.1)   -  round(third_stat_Met     ,0.1)),0.1);
      diff7   = round((round(stat7,0.1)   -  round(first_stat_Placebo ,0.1)),0.1);
      diff8   = round((round(stat8,0.1)   -  round(second_stat_Placebo,0.1)),0.1);
      diff9   = round((round(stat9,0.1)   -  round(third_stat_Placebo, 0.1)),0.1);
          char_diff1  = strip(put(diff1,8.1))  || " ( " || strip(put(diff2,8.1)) || " to " ||
strip(put(diff3,8.1)) || " ) ";
          char_diff2  = strip(put(diff4,8.1))  || " ( " || strip(put(diff5,8.1)) || " to " ||
strip(put(diff6,8.1)) || " ) ";
          char_diff3  = strip(put(diff7,8.1))  || " ( " || strip(put(diff8,8.1)) || " to " ||
strip(put(diff9,8.1)) || " ) ";
  end;
  label
     char_stat1         = "Vitamin E (n=50) N(%) or mean(95% CI) [Manuscript]"
     char_compare_stat1 = "Vitamin E (n=50) N(%) or mean(95% CI) [DSIC]      "
     char_diff1         = "Vitamin E (n=50) N(%) or mean(95% CI) [Difference]"
     char_stat2         = "Metfomin (n=50) N(%) or mean(95% CI) [Manuscript]"
     char_compare_stat2 = "Metfomin (n=50) N(%) or mean(95% CI) [DSIC]      "
     char_diff2         = "Metfomin (n=50) N(%) or mean(95% CI) [Difference]"
     char_stat3         = "Placebo (n=47) N(%) or mean(95% CI) [Manuscript]"
     char_compare_stat3 = "Placebo (n=47) N(%) or mean(95% CI) [DSIC]      "
     char_diff3         = "Placebo (n=47) N(%) or mean(95% CI) [Difference]"
  ;

*proc print data = combined_table3_dataset(keep =table_name char_diff1-char_diff3  char_stat1-
char_stat3 char_compare_stat1-char_compare_stat3);
*  title3 'combined_table3_dataset';
*proc freq data = combined_table3_dataset;
*  tables diff1-diff9/list missing;


*******************************************************************************;
*************** Check Table 4 ************************************************;
*******************************************************************************;


DATA TABLE4;
  SET table4;
  if ALT ne .;

proc freq data = table4;
  table tx/list missing;
%baseline_univariate(table3,dfibro      );

%baseline_univariate(table4,calt       );
%baseline_univariate(table4,cast       );
%baseline_univariate(table4,cggt       );
%baseline_univariate(table4,calka      );
%baseline_univariate(table4,cbilit     );
```

```
%baseline_univariate(table4,cvite      );
%baseline_univariate(table4,ctrig      );
%baseline_univariate(table4,cchol      );
%baseline_univariate(table4,chdl       );
%baseline_univariate(table4,cldl       );
%baseline_univariate(table4,choma      );
%baseline_univariate(table4,cgluc      );
%baseline_univariate(table4,cweight    );
%baseline_univariate(table4,cwaist     );
%baseline_univariate(table4,cbmi       );
%baseline_univariate(table4,cbmiz      );
%baseline_univariate(table4,ctotalf    );
%baseline_univariate(table4,ctanner    );
%baseline_univariate(table4,chlth      );
%baseline_univariate(table4,cpsych     );
%baseline_univariate(table4,cphlth     );
%baseline_univariate(table4,cppsych    );

data compare_table4_uni;
  set
calt_univariate
cast_univariate
cggt_univariate
calka_univariate
cbilit_univariate
cvite_univariate
ctrig_univariate
cchol_univariate
chdl_univariate
cldl_univariate
choma_univariate
cgluc_univariate
cweight_univariate
cwaist_univariate
cbmi_univariate
cbmiz_univariate
ctotalf_univariate
ctanner_univariate
chlth_univariate
cpsych_univariate
cphlth_univariate
cppsych_univariate
;

proc print data = compare_table4_uni;
  title3 'compare_table4_uni';

data compare_table4;
  set  compare_table4_uni;
  length char_compare_stat1-char_compare_stat3 $ 30.;
  if table_name in ('CBMIZ' 'CBILIT') then do;
         char_compare_stat1 = strip(put(first_stat_VitE   ,8.2))  || " ( " ||
strip(put(second_stat_VitE   ,8.2)) || " to "  || strip(put(third_stat_VitE   ,8.2)) ||" ) ";
         char_compare_stat2 = strip(put(first_stat_Met    ,8.2))  || " ( " ||
strip(put(second_stat_Met    ,8.2)) || " to "  || strip(put(third_stat_Met    ,8.2)) ||" ) ";
         char_compare_stat3 = strip(put(first_stat_Placebo,8.2))  || " ( " ||
strip(put(second_stat_Placebo,8.2)) || " to "  || strip(put(third_stat_Placebo,8.2)) ||" ) ";
  end;
  else do;
         char_compare_stat1 = strip(put(first_stat_VitE   ,8.1))  || " ( " ||
strip(put(second_stat_VitE   ,8.1)) || " to "  || strip(put(third_stat_VitE   ,8.1)) ||" ) ";
         char_compare_stat2 = strip(put(first_stat_Met    ,8.1))  || " ( " ||
strip(put(second_stat_Met    ,8.1)) || " to "  || strip(put(third_stat_Met    ,8.1)) ||" ) ";
         char_compare_stat3 = strip(put(first_stat_Placebo,8.1))  || " ( " ||
strip(put(second_stat_Placebo,8.1)) || " to "  || strip(put(third_stat_Placebo,8.1)) ||" ) ";
  end;
proc print data = compare_table4;
  title3 'compare_table4';

*** Importing the Table 4 Data taken from the primary outcome paper;
data table4_data;
```

```
  infile table4 delimiter = ',' MISSOVER DSD  firstobs=2 ls=1080;
  length characteristic $45 table_name $30 char_stat1-char_stat3 $23 ;
  input
  characteristic $ table_name $ stat1 stat2   stat3   stat4   stat5   stat6   stat7   stat8 stat9
char_stat1 $   char_stat2 $   char_stat3 $
;
  if lengthn(characteristic) NE 0 then output table4_data;

data table4_data;
  set table4_data;
  sort_order = _n_;
  table_name = upcase(table_name);

*** Merging the DSIC Table 4 data and the Table 3 data from the manuscript;
*** Creating variables to calculate the difference between the datasets;
proc sort data = compare_table4;
  by  table_name  ;
proc sort data = table4_data;
  by  table_name  ;

data combined_table4_dataset;
  merge compare_table4 (in = in1)
        table4_data     (in = in2)
        ;
  by table_name  ;
  if in1 and in2 then output combined_table4_dataset;

data combined_table4_dataset;
  set combined_table4_dataset;
  length char_diff1-char_diff3 $ 30.;

  if table_name in ('CBMIZ' 'CBILIT') then do;
      diff1   = round((round(stat1,0.01)   -  round(first_stat_VitE    ,0.01)),0.01);
      diff2   = round((round(stat2,0.01)   -  round(second_stat_VitE   ,0.01)),0.01);
      diff3   = round((round(stat3,0.01)   -  round(third_stat_VitE    ,0.01)),0.01);
      diff4   = round((round(stat4,0.01)   -  round(first_stat_Met     ,0.01)),0.01);
      diff5   = round((round(stat5,0.01)   -  round(second_stat_Met    ,0.01)),0.01);
      diff6   = round((round(stat6,0.01)   -  round(third_stat_Met     ,0.01)),0.01);
      diff7   = round((round(stat7,0.01)   -  round(first_stat_Placebo ,0.01)),0.01);
      diff8   = round((round(stat8,0.01)   -  round(second_stat_Placebo,0.01)),0.01);
      diff9   = round((round(stat9,0.01)   -  round(third_stat_Placebo, 0.01)),0.01);
           char_diff1  = strip(put(diff1,8.2))  || " ( " || strip(put(diff2,8.2)) || " to " ||
strip(put(diff3,8.2)) || " ) ";
           char_diff2  = strip(put(diff4,8.2))  || " ( " || strip(put(diff5,8.2)) || " to " ||
strip(put(diff6,8.2)) || " ) ";
           char_diff3  = strip(put(diff7,8.2))  || " ( " || strip(put(diff8,8.2)) || " to " ||
strip(put(diff9,8.2)) || " ) ";
  end;

  else do;
      diff1   = round((round(stat1,0.1)   -  round(first_stat_VitE    ,0.1)),0.1);
      diff2   = round((round(stat2,0.1)   -  round(second_stat_VitE   ,0.1)),0.1);
      diff3   = round((round(stat3,0.1)   -  round(third_stat_VitE    ,0.1)),0.1);
      diff4   = round((round(stat4,0.1)   -  round(first_stat_Met     ,0.1)),0.1);
      diff5   = round((round(stat5,0.1)   -  round(second_stat_Met    ,0.1)),0.1);
      diff6   = round((round(stat6,0.1)   -  round(third_stat_Met     ,0.1)),0.1);
      diff7   = round((round(stat7,0.1)   -  round(first_stat_Placebo ,0.1)),0.1);
      diff8   = round((round(stat8,0.1)   -  round(second_stat_Placebo,0.1)),0.1);
      diff9   = round((round(stat9,0.1)   -  round(third_stat_Placebo, 0.1)),0.1);
           char_diff1  = strip(put(diff1,8.1))  || " ( " || strip(put(diff2,8.1)) || " to " ||
strip(put(diff3,8.1)) || " ) ";
           char_diff2  = strip(put(diff4,8.1))  || " ( " || strip(put(diff5,8.1)) || " to " ||
strip(put(diff6,8.1)) || " ) ";
           char_diff3  = strip(put(diff7,8.1))  || " ( " || strip(put(diff8,8.1)) || " to " ||
strip(put(diff9,8.1)) || " ) ";
  end;
  label
     char_stat1         = "Vitamin E (n=50) mean(95% CI) [Manuscript]"
     char_compare_stat1 = "Vitamin E (n=50) mean(95% CI) [DSIC]      "
     char_diff1         = "Vitamin E (n=50) mean(95% CI) [Difference]"
     char_stat2         = "Metfomin (n=51) mean(95% CI) [Manuscript]"
```

```
     char_compare_stat2 = "Metfomin (n=51) mean(95% CI) [DSIC]      "
     char_diff2         = "Metfomin (n=51 mean(95% CI)) [Difference]"
     char_stat3         = "Placebo (n=49) mean(95% CI) [Manuscript]"
     char_compare_stat3 = "Placebo (n=49) mean(95% CI) [DSIC]      "
     char_diff3         = "Placebo (n=49) mean(95% CI) [Difference]"
  ;

/*
proc print data = combined_table4_dataset(keep =table_name char_diff1-char_diff3  char_stat1-
char_stat3 char_compare_stat1-char_compare_stat3);
  title3 'combined_table4_dataset';
proc freq data = combined_table4_dataset;
  tables diff1-diff9/list missing;
*/


proc sort data = combined_table1_dataset;
  by sort_order;

ods csv file = out_t1;
run;

proc print data = combined_table1_dataset NOOBS label;
       var characteristic
char_stat1
char_compare_stat1
char_diff1
char_stat2
char_compare_stat2
char_diff2
char_stat3
char_compare_stat3
char_diff3
;
       title3 "DSIC Check of Table 1: Baseline Characteristics by Treatment Group";
run;


proc sort data = combined_table2_dataset;
  by sort_order;

ods csv file = out_t2;
run;

proc print data = combined_table2_dataset NOOBS label;
       var characteristic
char_stat1
char_compare_stat1
char_diff1
char_stat2
char_compare_stat2
char_diff2
char_stat3
char_compare_stat3
char_diff3
;
       title3 "DSIC Check of Table 2: Primary Outcome: Sustained Reduction in ALT Level by
Treatment Group";
run;

proc sort data = combined_table3_dataset;
  by sort_order;

ods csv file = out_t3;
run;

proc print data = combined_table3_dataset NOOBS label;
       var characteristic
char_stat1
char_compare_stat1
char_diff1
```

```
char_stat2
char_compare_stat2
char_diff2
char_stat3
char_compare_stat3
char_diff3
;
       title3 "DSIC Check of Table 3: Change From Baseline to End of Treatment in Liver
Histology by Treatment Group";
run;



proc sort data = combined_table4_dataset;
  by sort_order;

ods csv file = out_t4;
run;

proc print data = combined_table4_dataset NOOBS label;
       var characteristic
char_stat1
char_compare_stat1
char_diff1
char_stat2
char_compare_stat2
char_diff2
char_stat3
char_compare_stat3
char_diff3
;
       title3 "DSIC Check of Table 4: Change From Baseline to End of Treatment in Serum
Biochemistry Test Results, Lipid Levels, Metabolic Characteristics, and Quality ofLife by
Treatment Group";
run;
```