Dataset Integrity Check for the HALT-PKD Data 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

The HALT-PKD study was a large randomized clinical trial to determine the impact of intensive blockade of the renin-angiotensin-aldosterone system (RAAS) and the level of blood pressure control on progressive renal disease in individuals with early and more advanced stages of autosomal dominant polycystic kidney disease (ADPKD). In Study A, participants with a glomerular filtration rate (GFR) greater than 60 mL/min/1.73 m_2, will be randomized to one of four conditions in a 2-by-2 design: combination angiotensin -converting enzyme inhibitor (ACE-I) and angiotensin receptor blocker (ARB) therapy at two levels of blood pressure control (standard, systolic 120-130 and diastolic 70-80 mm Hg vs. low, systolic 95-110 and diastolic 60-75 mm Hg) or ACE-I monotherapy at the same two levels of blood pressure control. The primary outcome of Study A is the percent change in total kidney volume, as measured by magnetic resonance imaging (MR). Study B will assess the effects of intensive blockade of the RAAS through combination ACE-I/ARB therapy as compared with ACE-I monotherapy, with both groups treated to a standard level of blood pressure control (systolic 110130 mm Hg and diastolic 80 mm Hg) . The primary outcome for Study B is a composite endpoint of time to the 50% reduction of baseline eGFR, ESRD or death.

3 Archived Datasets

All SAS data files, as provided by the Data Coordinating Center (DCC), are located in the "Data" folder in the data package. For this replication, variables were taken from those datasets only.

4 Statistical Methods

Analyses were performed to duplicate the results for the data published in 2 papers in The New England Journal of Medicine in November 2014: the first by Schrier, et al.; and the second by Torres, et al. To verify the integrity of the datasets, Tables 1 and 2 in both of the papers were checked.

5 Results

- Table A lists the variables that were used in the replication of Study A Table 1.
- Table B compares the results calculated from the provided data files to the results published in Study A Table 1.
- Table C lists the variables that were used in the replication of Study A Table 2.
- Table D compares the results calculated from the provided data files to the results published in Study A Table 2.
- Table E lists the variables that were used in the replication of Study B Table 1.
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- Figure A compares the results calculated from the provided data files to the results published in Study B Figure 3.
- Table J compares the results calculated from the provided data files to the results published in Study B Figure 3.

6 Conclusions

The NIDDK repository is confident that the HALT_PKD data files to be distributed are a copy of the manuscript data with only inconsequential discrepancies.

7 References

[1]Schrier, Robert, et al. “Blood Pressure in Early Autosomal Dominant Polycystic Kidney Disease.” The New England Journal of Medicine. DOI: 10.1056/NEJMoa1402685

[2]Torres, Vincente E., et al. "Angiotensin Blockade in Late Autosomal Dominant Polycystic Kidney Disease." The New England Journal of Medicine. DOI: 10.1056/NEJMoa1402686.

Table A: Variables used to replicate Study ATable 1: Demographic, Clinical, and Laboratory Characteristics at Baseline, According to Study Group of the 2-by-2 Factorial Design Trial.

Characteristic	Variable(s)
Grouping of Treatment: Lisinopril vs Placebo	Baseline.study
Grouping of Blood Pressue	Baseline.randtype
Age (years)	Baseline.age
Male sex	Baseline.sex
Race – White	Baseline.racee
Race - Black	Baseline.raced
Race – Other	Baseline.racea,raceb,racec,racef
Race- Data missing	Baseline.racea, raceb, racec, raced, racee, racef, raceg
PKD genotype	Genetype09022014.genetype
Body-mass index	Baseline.bmi
Estimated GFR – ml/min/1.73 m^2	Baseline.ckd_epi_egfr
Urinary aldosterone – ug/24 hr	Baseline.ualdos
Urinary albumin – mg/24 hr	Baseline.ualbum
Total kidney volume – ml	Baseline.tkv
Renal blood flow – ml/min/1.73 m^2	Baseline.rbf_modify
Left-ventricular-mass index – g/m^2	Baseline.lvmi

Table B: Comparison of integrity check values to Study A reference article Table 1 values

Characteristic	Manuscript Lisinopril-Telmisartan (N=273)	DSIC Lisinopril-Telmisartan (N=273)	Manuscript Lisinopril-Placebo (N=285)	DSIC Lisinopril-Placebo (N=285)	DIFF
Age – yr	37.0±8.3	37.0±8.3	36.3±8.3	36.3±8.3	0
Male sex – no. (%)	141 (51.6)	141 (51.6)	142 (49.8)	142 (49.8)	0
Race – no. (%)					0
White	255 (93.4)	255 (93.4)	262 (91.9)	262 (91.9)	0
Black	6 (2.2)	6 (2.2)	8 (2.8)	8 (2.8)	0
Other	10 (3.7)	10 (3.7)	17 (6.0)	17 (6.0)	0
Data missing	2 (0.7)	2 (0.7)	0	0	0
PKD genotype – no./total no. (%)					0
PKD1	190/252 (75.4)	190/252 (75.4)	192/260 (73.8)	192/260 (73.8)	0
PKD2	42/252 (16.7)	42/252 (16.7)	42/260 (16.2)	42/260 (16.2)	0
No mutation detected	20/252 (7.9)	20/252 (7.9)	26/260 (10.0)	26/260 (10.0)	0
Body-mass index	27.4±5.2	27.4±5.2	27.1±5.1	27.1±5.1	0
Estimated GFR – ml/min/1.73 m^2	90.4±17.5	90.4±17.5	92.6±17.4	92.6±17.4	0
Urinary aldosterone – ug/24 hr	12.2±10.0	12.2±10.0	12.2±9.1	12.2±9.1	0
Urinary albumin – mg/24 hr					0
Median	19.3	19.3	17.6	17.6	0
Interquartile range	12.7–35.2	12.7–35.2	11.7–30.6	11.7–30.6	0
Total kidney volume – ml	1264.6±786.2	1264.6±786.2	1164.0±661.0	1164.0±661.0	0
Renal blood flow – ml/min/1.73 m^2	607.7±195.3	607.7±195.3	609.2±216.2	609.2±216.2	0
Left-ventricular-mass index –g/m^2	64.1±13.2	64.1±13.2	63.7±12.9	63.7±12.9	0

Characteristic	Manuscript Standard Blood Pressure (N=284)	DSIC Standard Blood Pressure (N=284)	Manuscript Low Blood Pressue (N=274)	DSIC Low Blood Pressue (N=274)	DIFF
Age – yr	36.3±8.4	36.3±8.4	36.9±8.2	36.9±8.2	0
Male sex – no. (%)	143 (50.4)	143 (50.4)	140 (51.1)	140 (51.1)	0
Race – no. (%)					0
White	258 (90.8)	258 (90.8)	259 (94.5)	259 (94.5)	0
Black	7 (2.5)	7 (2.5)	7 (2.6)	7 (2.6)	0
Other	18 (6.3)	18 (6.3)	9 (3.3)	9 (3.3)	0
Data missing	2 (0.7)	2 (0.7)	0	0	0
PKD genotype – no./total no. (%)					0
PKD1	204/260 (78.5)	204/260 (78.5)	178/252 (70.6)	178/252 (70.6)	0
PKD2	34/260 (13.1)	34/260 (13.1)	50/252 (19.8)	50/252 (19.8)	0
No mutation detected	22/260 (8.5)	22/260 (8.5)	24/252 (9.5)	24/252 (9.5)	0
Body-mass index	27.3±5.4	27.3±5.4	27.1±4.9	27.1±4.9	0
Estimated GFR – ml/min/1.73 m^2	91.7±17.8	91.7±17.8	91.4±17.2	91.4±17.2	0
Urinary aldosterone – ug/24 hr	13.0±10.6	13.0±10.6	11.4±8.2	11.4±8.2	0
Urinary albumin – mg/24 hr					0
Median	19.1	19.1	17.7	17.7	0
Interquartile range	12.8–31.8	12.8–31.8	11.7–33.3	11.7–33.3	0
Total kidney volume – ml	1240.6±747.1	1240.6±747.1	1185.2±704.0	1185.2±704.0	0
Renal blood flow – ml/min/1.73 m^2	592.4±206.1	592.4±206.1	624.7±205.3	624.7±205.3	0
Left-ventricular-mass index –g/m^2	63.8±13.8	63.8±13.8	63.9±12.2	63.9±12.2	0

Table C: Variables used to replicate Study A Table 2: Adverse Events in the 2-by-2 Factorial Design Trial.

Characteristic	Variable(s)
Grouping of Treatment: Lisinopril vs Placebo	Baseline.study_t
Grouping of Blood Pressue	Baseline.randtype
Mean follow-up – yr	Safety.yrsInStudyModified
Acute kidney injury – No. of events, No. of participants	Safety.countAKI, Safety.indAKI
Hyperkalemia – No. of events, No. of participants	Safety.hprk_any, Safety.ind_hprk_any
Hospitalizations – No. of events, Incidence – no. of events/100 person-yr	Safety.no_hospitalizations, Safety.yrsInStudyModified
Cardiac-related hospitalization – No. of events, Incidence – no. of events/100 person-yr	Safety.no_cardiac_hospitalizations, , Safety.yrsInStudyModified
Cancer – No. of events, No. of participants (%)	Safety.count_nonmelskincancer, Safety.count-melanoma, Safety.count_othercancer, Safety.ind_nonmelskincancer, Safety.ind_melanoma, Safety.ind_othercancer
Death – no. of participants	Safety.died
Cardiac disorder – No. of events, No. of participants	Safety.count_cardiac, Safety.ind_cardiac
Gastrointestinal disorder – No. of events, No. of participants	Safety.count_gastro, Safety.ind_gastro
Abdominal pain – No. of events, No. of participants	Safety.count_abdominalPain, Safety.ind_abdominalPain
Nervous system disorder – No. of events, No. of participants	Safety.count_nervous, Safety.ind_nervous
Renal or urinary system disorder – No. of events, No. of participants	Safety.count_renal, Safety.ind_renal
Nephrolithiasis or renal colic – No. of events, No. of participants	Safety.count_renalColic, Safety.ind_renalColic

Table D: Comparison of integrity check values to Study A reference article Table 2 values

Event	Manuscript Lisinopril-Telmisartan (N=273)	DSIC Lisinopril-Telmisartan (N=273)	Manuscript Lisinopril-Placebo (N=285)	DSIC Lisinopril-Placebo (N=285)	DIFF
Mean follow-up – yr	5.6	5.6	5.7	5.7	0
Acute kidney injury					
No. of events	15	15	19	19	0
No. of participants - %	13 (4.8)	13 (4.8)	16 (5.6)	16 (5.6)	0
Hyperkalemia					
No. of events	13	13	6	6	0
No. of participants - %	11 (4.0)	11 (4.0)	5 (1.8)	5 (1.8)	0
Hospitalization					
No. of events	85	85	128	128	0
Incidence – no. of events/100	5.55	5.55	7.92	7.92	0
Cardiac-related hospitalization					
No. of events	13	13	9	9	0
Incidence – no. of events/100	0.85	0.85	0.56	0.56	0
Cancer					
No. of events	4	4	4	4	0
No. of participants - %	4 (1.5)	4 (1.5)	4 (1.4)	4 (1.4)	0
Serious adverse event					
Death - no. of participants - %	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)	0
Cardiac disorder					
No. of events	9	9	6	6	0
No. of participants - %	6 (2.2)	6 (2.2)	5 (1.8)	5 (1.8)	0
Gastrointestinal disorder					
No. of events	11	11	17	17	0
No. of participants - %	8 (2.9)	8 (2.9)	12 (4.2)	12 (4.2)	0
Abdominal pain					
No. of events	3	3	9	9	0
No. of participants - %	3 (1.1)	3 (1.1)	6 (2.1)	6 (2.1)	0
Nervous system disorder					
No. of events	10	10	12	12	0
No. of participants - %	8 (2.9)	8 (2.9)	10 (3.5)	10 (3.5)	0
Renal or urinary system disorder					
No. of events	14	14	15	15	0
No. of participants - %	12 (4.4)	12 (4.4)	14 (4.9)	14 (4.9)	0
Nephrolithiasis or renal colic					
No. of events	3	3	4	4	0
No. of participants - %	3 (1.1)	3 (1.1)	4 (1.4)	4 (1.4)	0

Event	Manuscript Standard Blood Pressure (N=284)	DSIC Standard Blood Pressure (N=284)	Manuscript Low Blood Pressue (N=274)	DSIC Low Blood Pressue (N=274)	DIFF
Mean follow-up – yr	5.7	5.7	5.6	5.6	0
Acute kidney injury					
No. of events	17	17	17	17	0
No. of participants - %	13 (4.6)	13 (4.6)	16 (5.8)	16 (5.8)	0
Hyperkalemia					
No. of events	11	11	8	8	0
No. of participants - %	9 (3.2)	9 (3.2)	7 (2.6)	7 (2.6)	0
Hospitalization					
No. of events	120	120	93	93	0
Incidence – no. of events/100 person-yr	7.43	7.43	6.07	6.07	0
Cardiac-related hospitalization					
No. of events	13	13	9	9	0
Incidence – no. of events/100 person-yr	0.80	0.80	0.59	0.59	0
Cancer					
No. of events	2	2	6	6	0
No. of participants - %	2 (0.7)	2 (0.7)	6 (2.2)	6 (2.2)	0
Serious adverse event					
Death - no. of participants - %	2 (0.7)	2 (0.7)	0	0	0
Cardiac disorder					
No. of events	12	12	3	3	0
No. of participants - %	8 (2.8)	8 (2.8)	3 (1.1)	3 (1.1)	0
Gastrointestinal disorder					
No. of events	21	21	7	7	0
No. of participants - %	16 (5.6)	16 (5.6)	4 (1.5)	4 (1.5)	0
Abdominal pain					
No. of events	7	7	5	5	0
No. of participants - %	6 (2.1)	6 (2.1)	3 (1.1)	3 (1.1)	0
Nervous system disorder					
No. of events	14	14	8	8	0
No. of participants - %	11 (3.9)	11 (3.9)	7 (2.6)	7 (2.6)	0
Renal or urinary system disorder					
No. of events	16	16	13	13	0
No. of participants - %	14 (4.9)	14 (4.9)	12 (4.4)	12 (4.4)	0
Nephrolithiasis or renal colic					
No. of events	7	7	0	0	0
No. of participants - %	7 (2.5)	7 (2.5)	0	0	0

Table E: Variables used to replicate Study B Table 1: Demographic, Clinical, and Laboratory Characteristics of the Participants at Baseline.

Characteristic	Variable(s)
Grouping of Treatment: Lisinopril vs Placebo	Baseline.study
Age (years)	Baseline.age
Male sex	Baseline.sex
Race - White	Baseline.racee
Race - Black	Baseline.raced
Race - Other	Baseline.racea,raceb,racec,racef
PKD genotype	Genetype09022014.genetype
Body-mass index:	Baseline.bmi
Serum creatinine – mg/dl	Baseline.serumCreat_avg
Estimated GFR – ml/min/1.73 m^2	Baseline.ckd_epi_egfr
Urinary sodium – mmol/24 hr	Baseline.usodium
Urinary aldosterone – ug/24 hr	Baseline.ualdos
Urinary albumin – mg/24 hr	Baseline.ualbum

Table F: Comparison of integrity check values to Study B reference article Table 1 values

Characteristic	Manuscript Lisinopril-Telmisartan (N=244)	DSIC Lisinopril-Telmisartan (N=244)	Manuscript Lisinopril-Placebo (N=242)	DSIC Lisinopril-Placebo (N=242)	DIFF
Age – yr	48.6±8.5	48.6±8.5	48.9±8.1	48.9±8.1	0
Male sex – no. (%)	115 (47.1)	115 (47.1)	120 (49.6)	120 (49.6)	0
Race – no. (%)					0
White	230 (94.3)	230 (94.3)	224 (92.6)	224 (92.6)	0
Black	5 (2.0)	5 (2.0)	7 (2.9)	7 (2.9)	0
Other	9 (3.7)	8 (3.3)	11 (4.5)	11 (4.5)	-1
PKD genotype – no./total no. (%)					0
PKD1	179/223 (80.3)	179/223	183/224 (81.7)	183/224 (81.7)	0
PKD2	30/223 (13.5)	30/223	30/224 (13.4)	30/224 (13.4)	0
No mutation detected	14/223 (6.3)	14/223 (6.3)	11/224 (4.9)	11/224 (4.9)	0
Body-mass index	28.0±4.9	28.0±4.9	28.0±5.5	28.0±5.5	0
Serum creatinine – mg/dl	1.5±0.4	1.5±0.4	1.6±0.4	1.6±0.4	
Estimated GFR – ml/min/1.73 m^2	48.5±11.5	48.5±11.5	47.9±12.2	47.9±12.2	0
Urinary sodium – mmol/24 hr	177.4±78.2	177.4±78.2	178.2±84.0	178.2±84.0	
Urinary aldosterone – ug/24 hr	10.2±8.4	10.2±8.4	9.1±5.8	9.1±5.8	0
Urinary albumin – mg/24 hr					0
Median	29.7	29.7	28.1	28.1	0
Interquartile range	16.6–71.8	16.6–71.8	17.3–78.0	17.3–78.0	0

Table G: Variables used to replicate Study B Table 2: Serious Adverse Events.

Characteristic	Variable(s)
Grouping of Treatment: Lisinopril vs Placebo	Baseline.study_t
Mean duration of follow-up – yr	Safety.yrsInStudyModified
Death – no. of participants	Safety.died
Cardiac disorder – No. of events, No. of participants	Safety.count_cardiac, Safety.ind_cardiac
Coronary artery disease – No. of events, No. of participants	Safety. count_coronaryArteryDisease, Safety. ind_coronaryArteryDisease
Arrhythmia - No. of events, No. of participants	Safety.count_ arrhythmias, Safety.ind_ arrhythmias
Other - No. of events, No. of participants	Safety. count_otherCardiacDisorder, Safety.ind_otherCardiacDisorder
Gastrointestinal disorder – No. of events, No. of participants	Safety.count_gastro, Safety.ind_gastro
Nervous system disorder – No. of events, No. of participants	Safety.count_nervous, Safety.ind_nervous
Cerebrovascular event – No. of events, No. of participants	Safety.count_ cerebrovascular, Safety.ind_ cerebrovascular
Headache – No. of events, No. of participants	Safety.count_headache, Safety.ind_headache
Other – No. of events, No. of participants	Safety.count_ otherNervousSystemDisorder + Safety.count_syncope, Safety.ind_ otherNervousSystemDisorder + Safety.ind_syncope
Renal or urinary system disorder – No. of events, No. of participants	Safety.count_renal, Safety.ind_renal
Renal hemorrhage or hematuria – No. of events, No. of participants	Safety.count_ renalHemorrhage, Safety.ind_ renalHemorrhage
Nephrolithiasis or renal colic – No. of events, No. of participants	Safety.count_renalColic, Safety.ind_renalColic
Acute kidney injury – No. of events, No. of participants	Safety.count_acuteKidneyInjury, Safety.ind_ acuteKidneyInjury
Other – No. of events, No. of participants	Safety.count_ otherRenalSystemDisorder +Safety.count_ urinaryTractObstruct, Safety.ind_ otherRenalSystemDisorder +Safety. urinaryTractObstruct

Table H: Comparison of integrity check values to Study B reference article Table 2 values

Event	Manuscript Lisinopril-Telmisartan (N=244)	DSIC Lisinopril-Telmisartan (N=244)	Manuscript Lisinopril-Placebo (N=242)	DSIC Lisinopril-Placebo (N=242)	DIFF
Mean duration of follow-up – yr	5.2	5.2	5.2	5.2	0
Death - no. of participants - %	4 (1.6)	4 (1.6)	5 (2.1)	5 (2.1)	0
Cardiac disorder					
No. of events	12	12	18	18	0
No. of participants - %	11 (4.5)	11 (4.5)	13 (5.4)	13 (5.4)	0
Coronary artery disease					
No. of events	3	3	9	9	0
No. of participants - %	3 (1.2)	3 (1.2)	9 (3.7)	9 (3.7)	0
Arrhythmia					
No. of events	5	5	6	6	0
No. of participants - %	4 (1.6)	4 (1.6)	3 (1.2)	3 (1.2)	0
Other					
No. of events	4	4	3	3	0
No. of participants - %	4 (1.6)	4 (1.6)	3 (1.2)	3 (1.2)	0
Gastrointestinal disorder					
No. of events	18	18	33	33	0
No. of participants - %	15 (6.1)	15 (6.1)	25 (10.3)	25 (10.3)	0
Nervous system disorder					
No. of events	9	9	10	10	0
No. of participants - %	8 (3.3)	8 (3.3)	9 (3.7)	9 (3.7)	0
Cerebrovascular event					
No. of events	4	4	3	3	0
No. of participants - %	4 (1.6)	4 (1.6)	3 (1.2)	3 (1.2)	0
Headache					
No. of events	2	2	2	2	0
No. of participants - %	2 (0.8)	2 (0.8)	2 (0.8)	2 (0.8)	0
Other					
No. of events	3	3	5	5	0
No. of participants - %	3 (1.2)	3 (1.2)	4 (1.7)	4 (1.7)	0
Renal or urinary system disorder					
No. of events	14	14	34	34	0
No. of participants - %	14 (5.7)	14 (5.7)	19 (7.9)	19 (7.9)	0
Renal hemorrhage or hematuria					
No. of events	5	5	2	2	0
No. of participants - %	5 (2.0)	5 (2.0)	2 (0.8)	2 (0.8)	0
Nephrolithiasis or renal colic					
No. of events	1	1	12	12	0
No. of participants - %	1 (0.4)	1 (0.4)	4 (1.7)	4 (1.7)	0

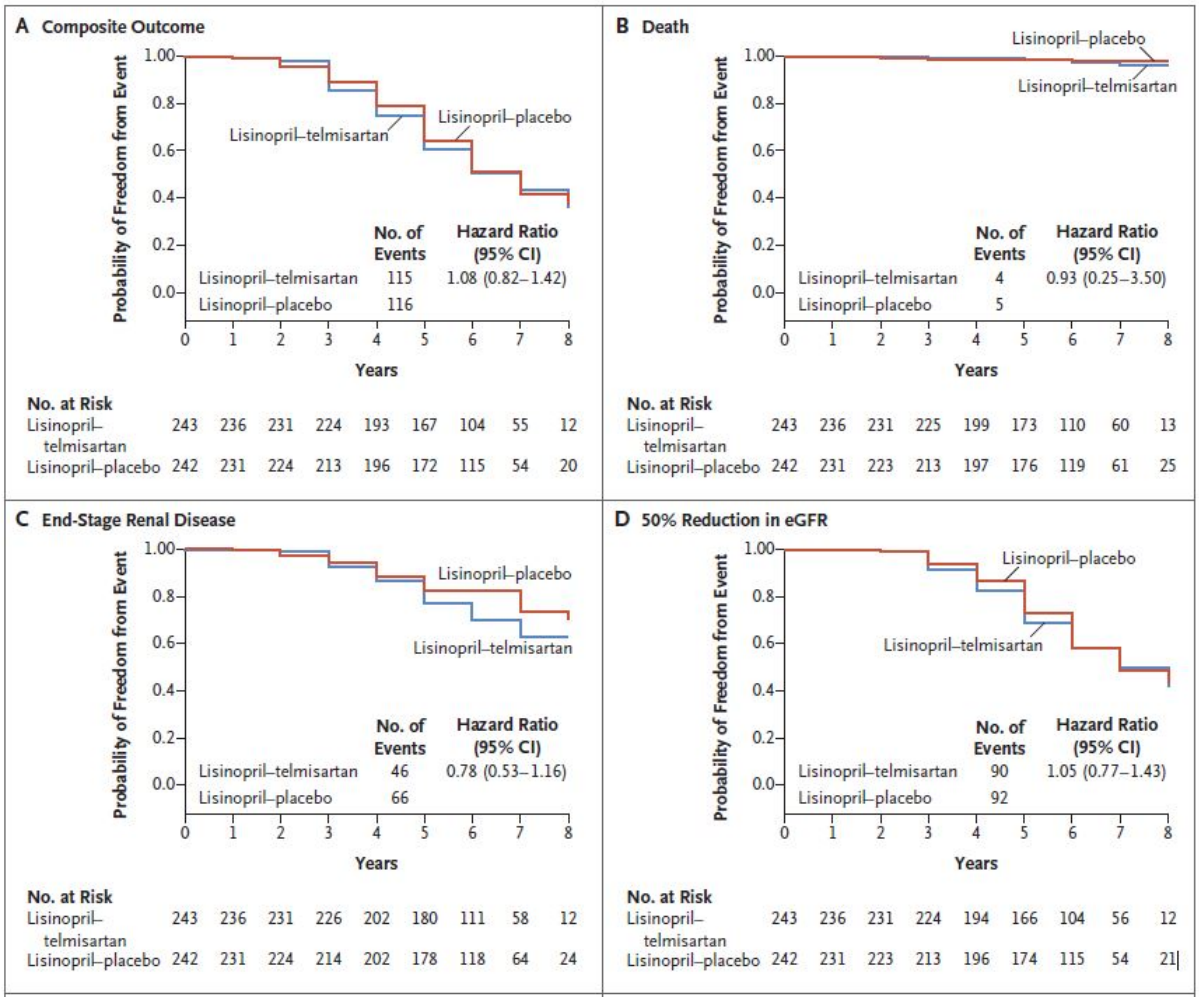
Event	Manuscript Lisinopril-Telmisartan (N=244)	DSIC Lisinopril-Telmisartan (N=244)	Manuscript Lisinopril-Placebo (N=242)	DSIC Lisinopril-Placebo (N=242)	DIFF
Acute kidney injury					
No. of events	3	3	5	5	0
No. of participants - %	3 (1.2)	3 (1.2)	5 (2.1)	5 (2.1)	0
Other					
No. of events	5	5	15	15	0
No. of participants - %	5 (2.0)	5 (2.0)	12 (5.0)	12 (5.0)	0

Table I: Variables Used to Replicate Study B Figure 3: Effect of Lisinopril-Telmisartan, as Compared with Lisinopril-Placebo, on the Time to Primary-Outcome Events and on the Estimated Glomerular Filtration Rate (eGFR)

Characteristic	Variable(s)
Composite Outcome	endpoints_sep2014.death, endpoints_sep2014.esrd, endpoints_sep2014.egfr_50
Death	endpoints_sep2014.death
End-Stage Renal Disease	endpoints_sep2014.esrd
50% Reduction in eGFR	endpoints_sep2014.egfr_50
No. at Risk – Composite Outcome	endpoints_sep2014.any_endpoint_date, endpoints_sep2014.b2date, endpoints_sep2014.lastVisit_rev, endpoints_sep2014.death, endpoints_sep2014.esrd, endpoints_sep2014.egfr_50
No. at Risk - Death	endpoints_sep2014.dthdate, endpoints_sep2014.b2date, endpoints_sep2014.lastVisit_rev, endpoints_sep2014.death
No. at Risk – ESRD	endpoints_sep2014.tosdate, endpoints_sep2014.b2date, endpoints_sep2014.lastVisit_rev, endpoints_sep2014.esrd
No. at Risk – 50% Reduction in eGFR	endpoints_sep2014.confsdate, endpoints_sep2014.b2date, endpoints_sep2014.lastVisit_rev, endpoints_sep2014.egfr_50

Figure A: Comparison of Values Computed in Integrity Check to Reference Article Figure 3 Values

Manuscript



DSIC

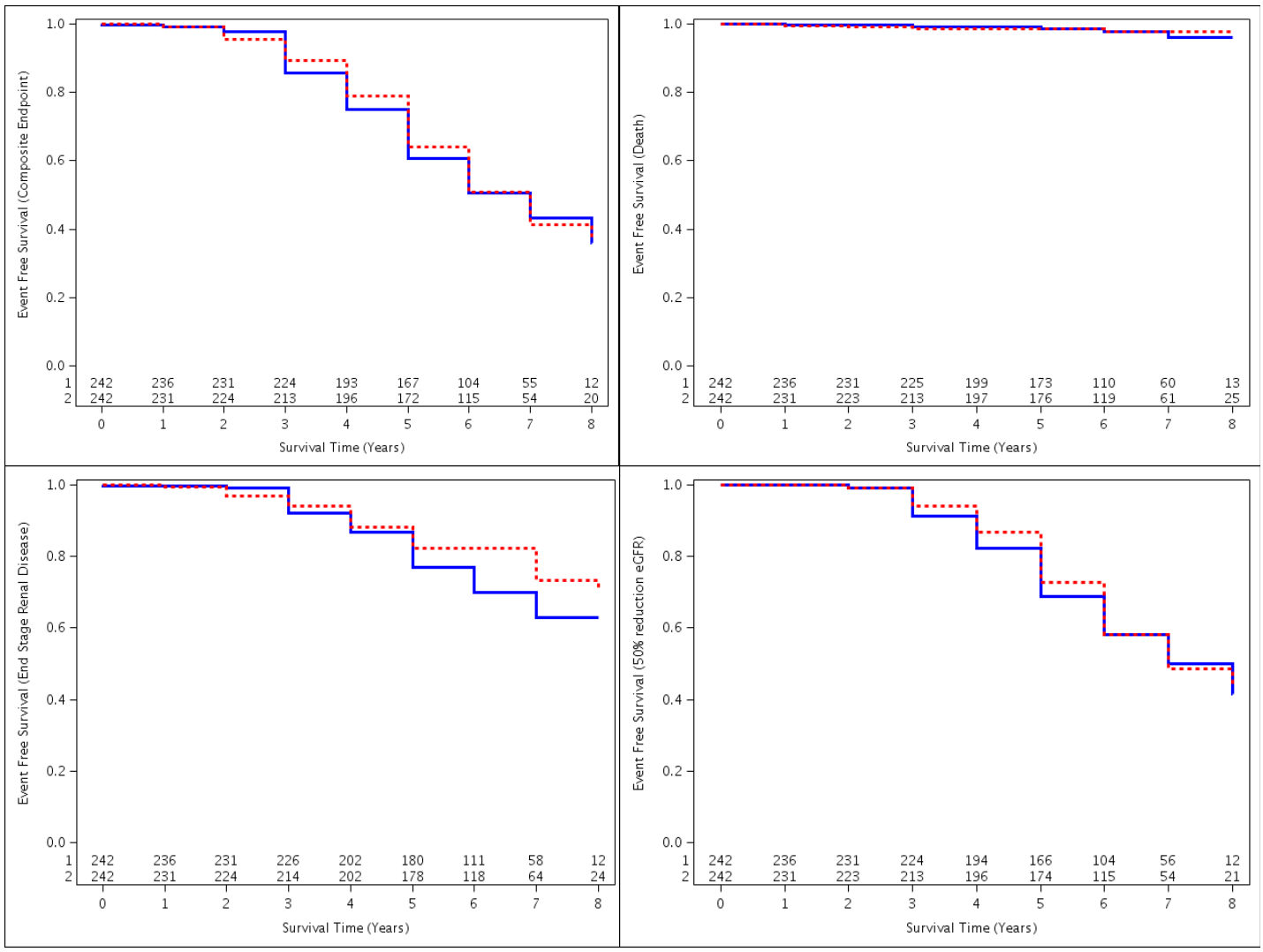

Event Free Survival (Composite Endpoint)
1.0
0.8
0.6
0.4
0.2
0.0
1 242 236 231 224 193 167 104 55 12
2 242 231 224 213 196 172 115 54 20
0 1 2 3 4 5 6 7 8
Survival Time (Years)
Event Free Survival (Death)
1.0
0.8
0.6
0.4
0.2
0.0
1 242 236 231 225 199 173 110 60 13
2 242 231 223 213 197 176 119 61 25
0 1 2 3 4 5 6 7 8
Survival Time (Years)
Event Free Survival (End Stage Renal Disease)
1.0
0.8
0.6
0.4
0.2
0.0
1 242 236 231 226 202 180 111 58 12
2 242 231 224 214 202 178 118 64 24
0 1 2 3 4 5 6 7 8
Survival Time (Years)
Event Free Survival (50% reduction eGFR)
1.0
0.8
0.6
0.4
0.2
0.0
1 242 236 231 224 194 166 104 56 12
2 242 231 223 213 196 174 115 54 21
0 1 2 3 4 5 6 7 8
Survival Time (Years)

Table J: Comparison of Values Computed in Integrity Check to Reference Article Figure 3 Values

No. of Events:

Event	Manuscript Lisinopril-telmisartan	DSIC Lisinopril-telmisartan	Difference	Manuscript Lisinopril-placebo	DSIC Lisinopril-placebo	Difference
Composite Outcome	115	115	0	116	116	0
Death	4	4	0	5	5	0
End-Stage Renal Disease	46	46	0	66	66	0
50% Reduction in eGFR	90	90	0	92	92	0

Hazard Ratio (95% CI):

Event	Manuscript	DSIC	Difference
Composite Outcome	1.08 (0.82-1.42)	1.08 (0.83-1.4)	0 (0.01-0.02)
Death	0.93 (0.25-3.50)	0.94 (0.25 – 3.56)	0.01 (0 – 0.06)
End-Stage Renal Disease	0.78 (0.53-1.16)	0.77 (0.53 – 1.14)	0.01 (0-0.02)
50% Reduction in eGFR	1.05 (0.77-1.43)	1.06 (0.79 – 1.42)	0.01 (0.02-0.01)

No. at Risk – Composite Outcome

Treatment Group	Year 0 Manuscript	Year 0 DSIC	Year 1 Manuscript	Year 1 DSIC	Year 2 Manuscript	Year 2 DSIC	Year 3 Manuscript	Year 3 DSIC	Year 4 Manuscript	Year 4 DSIC
Lisinopril-telmisartan	243	242	236	236	231	231	224	224	193	193
Lisinopril-placebo	242	242	231	231	224	224	213	213	196	196

Treatment Group	Year 5 Manuscript	Year 5 DSIC	Year 6 Manuscript	Year 6 DSIC	Year 7 Manuscript	Year 7 DSIC	Year 8 Manuscript	Year 8 DSIC
Lisinopril-telmisartan	167	167	104	104	55	55	12	12
Lisinopril-placebo	172	172	115	115	54	54	20	20

No. at Risk – Death

Treatment Group	Year 0 Manuscript	Year 0 DSIC	Year 1 Manuscript	Year 1 DSIC	Year 2 Manuscript	Year 2 DSIC	Year 3 Manuscript	Year 3 DSIC	Year 4 Manuscript	Year 4 DSIC
Lisinopril-telmisartan	243	242	236	236	231	231	225	225	199	199
Lisinopril-placebo	242	242	231	231	223	223	213	213	197	197

Treatment Group	Year 5 Manuscript	Year 5 DSIC	Year 6 Manuscript	Year 6 DSIC	Year 7 Manuscript	Year 7 DSIC	Year 8 Manuscript	Year 8 DSIC
Lisinopril-telmisartan	173	173	110	110	60	60	13	13
Lisinopril-placebo	176	176	119	119	61	61	25	25

No. at Risk – End-Stage Renal Disease

Treatment Group	Year 0 Manuscript	Year 0 DSIC	Year 1 Manuscript	Year 1 DSIC	Year 2 Manuscript	Year 2 DSIC	Year 3 Manuscript	Year 3 DSIC	Year 4 Manuscript	Year 4 DSIC
Lisinopril-telmisartan	243	242	236	236	231	231	226	226	202	202
Lisinopril-placebo	242	242	231	231	224	224	214	214	202	202

Treatment Group	Year 5 Manuscript	Year 5 DSIC	Year 6 Manuscript	Year 6 DSIC	Year 7 Manuscript	Year 7 DSIC	Year 8 Manuscript	Year 8 DSIC
Lisinopril-telmisartan	180	180	111	111	58	58	12	12
Lisinopril-placebo	178	178	118	118	64	64	24	24

No. at Risk – 50% Reduction in eGFR

Treatment Group	Year 0 Manuscript	Year 0 DSIC	Year 1 Manuscript	Year 1 DSIC	Year 2 Manuscript	Year 2 DSIC	Year 3 Manuscript	Year 3 DSIC	Year 4 Manuscript	Year 4 DSIC
Lisinopril-telmisartan	243	242	236	236	231	231	224	224	194	194
Lisinopril-placebo	242	242	231	231	223	223	213	213	196	196

Treatment Group	Year 5 Manuscript	Year 5 DSIC	Year 6 Manuscript	Year 6 DSIC	Year 7 Manuscript	Year 7 DSIC	Year 8 Manuscript	Year 8 DSIC
Lisinopril-telmisartan	166	166	104	104	56	56	12	12
Lisinopril-placebo	174	174	115	115	54	54	21	21

Appendix A – SAS code for Study A Integrity Check

```
%let flnm = %sysfunc(getoption(sysin));
title "Program saved as: &FLNM.";
title2 "Check HALT_PKD Study A input files for DSIC";

/*************************************************************************************************
*******************************
Programmer: Patty Griffin
Date: March 24, 2015

Function/Notes: Check HALT_PKD Study A input files for DSIC

Run with SAS v9.3 or later.

*************************************************************************************************
*******************************/
*  Input file  *;
****************;
libname inlib   "/prj/niddk/ims_analysis/HALT_PKD/private_orig_data/NIDDK/Study Data/Primary
Paper Analysis Data/Final SAS datasets/";
libname informs "/prj/niddk/ims_analysis/HALT_PKD/private_orig_data/NIDDK/Study Data/Non-CRF
Data/";
options nofmterr;

*************;
*  Formats  *;
*************;
proc format;


***********;
*  Macro  *;
***********;

%global caser;


*** Macro ***;
%macro freqdata1(order=, invar=, level=, levelname= );

data data0 data1;
  set _null_;

  proc freq data=table1 noprint;
    tables &invar*&caser/out=data0 outpct missing;
        format _all_;
        run;

data data1;
  set data0;
  length LEVEL $100 LEVELNAME $100;
  LEVEL=strip(&invar);
  LEVELNAME=strip(&levelname);


  data data1(keep=&caser name LEVEL LEVELNAME CHARALL ORDERER);
    set data1;
    length name $100 CHARALL $100;
    name=upcase("&invar");
    PCT_DISP=round(PCT_COL,.1);
    CHARALL=compress(put(COUNT,8.))||" ("||compress(put(PCT_DISP,8.1))||")";
    ORDERER=&order;
    if level in &level then output data1;

data accumfreq1;
  set accumfreq1 data1;

%mend freqdata1;
```

```
%macro meandata1(order=, invar=, roundvar=, digit=);
proc means data=table1 mean stddev  noprint;
       var &invar;
       class &caser;
       output out=data1 mean=mean stddev=stddev ;
       run;

data data1(drop=_TYPE_ _FREQ_ mean stddev );
  set data1;
  length name CHARALL $100;
  name=upcase("&invar");
  mean=round(mean,&roundvar);
  stddev=round(stddev,&roundvar);
  CHARALL=compress(put(mean,8.&digit))||" ± "||compress(put(stddev,8.&digit));
  ORDERER=&order;
  output;

data accummean1;
  set accummean1 data1;

%mend meandata1;

%macro mediandata1(order=, invar=, roundvar=, digit=);
proc means data=table1 median p25 p75 min max noprint;
       var &invar;
       class &caser;
       output out=data1 median=median p25=p25 p75=p75 min=min max=max;
       run;

data data1(drop=_TYPE_ _FREQ_ median p25 p75 min max);
  set data1;
  length name CHARALL $100;
  name=upcase("&invar");
  median=round(median,&roundvar);
  min=round(min,&roundvar);
  max=round(max,&roundvar);
  ORDERER=&order;
  CHARALL=compress(put(median,8.&digit));
  output;
  ORDERER=ORDERER+.01;
  *CHARALL=compress(put(min,8.&digit)||"-"||put(max,8.&digit));
  CHARALL=compress(put(p25,8.&digit)||","||put(p75,8.&digit));
  output;

data accummedian1;
  set accummedian1 data1;

%mend mediandata1;

%macro sumdata1(order=, invar=);
proc means data=table1 sum  noprint;
       var &invar;
       class &caser;
       output out=data1 sum=sum ;
       run;

data data1(drop=_TYPE_ _FREQ_ sum );
  set data1;
  length name CHARALL $100;
  name=upcase("&invar");
  CHARALL=compress(put(sum, 8.));
  ORDERER=&order;
  output;

data accumsum1;
  set accumsum1 data1;

%mend sumdata1;
```

```
%macro incidence100(order=, invar=, timevar=);
proc means data=table1 sum  noprint;
       var &invar &timevar;
       class &caser;
       output out=data1 sum=sum_events sum_time ;
       run;

data data1(drop=_TYPE_ _FREQ_ sum sum_events sum_time incidence);
  set data1;
  length name CHARALL $100;
  LEVELNAME = "Incidence";
   name=upcase("&invar");
  incidence=(sum_events/sum_time)*100;
  CHARALL=compress(put(incidence,4.2));
  ORDERER=&order;
  output;

data accumincid1;
  set accumincid1 data1;

%mend incidence100;

%macro inertdata1(order=);

data inert1;
  length orderer &caser 8.;
  orderer=&order.;
  &caser=-1;
  output;
  orderer=&order.;
  &caser=0;
  output;
  orderer=&order.;
  &caser=1;
  output;

data accuminert1;
  set accuminert1 inert1;

%mend inertdata1;


%macro datachunk();

%meandata1(order=1, invar=age, roundvar=.1, digit=1);
%freqdata1(order=2, invar=sex, level=(1), levelname="Male");
%freqdata1(order=3, invar=racee, level=(1), levelname="Race - White");
%freqdata1(order=4, invar=raced, level=(1), levelname="Race - Black");
%freqdata1(order=5, invar=race_other, level=(1), levelname="Race - Other");
%freqdata1(order=6, invar=race_missing, level=(1), levelname="Race - Data missing");
%meandata1(order=10, invar=bmi, roundvar=.1, digit=1);
%meandata1(order=11, invar=ckd_epi_egfr, roundvar=.1, digit=1);
%meandata1(order=12, invar=ualdos, roundvar=.1, digit=1);
%mediandata1(order=13, invar=ualbum, roundvar=.1, digit=1);
%meandata1(order=14, invar=TKV, roundvar=.1, digit=1);
%meandata1(order=15, invar=rbf_modify, roundvar=.1, digit=1);
%meandata1(order=16, invar=lvmi, roundvar=.1, digit=1);

%mend datachunk;

%macro datachunk2();

%meandata1(order=1, invar=yrsInStudyModified, roundvar=.1, digit=1);
%sumdata1(order=2,  invar=countAKI);
%freqdata1(order=3,  invar=indAKI, level=(1), levelname="AKI - No. of participants");
%sumdata1(order=4,  invar=hprk_any);
%freqdata1(order=5,  invar=ind_hprk_any, level=(1), levelname="Hyperkalemia - No. of
participants");
```

```
%sumdata1(order=6,  invar=no_hospitalizations);
%incidence100(order=7, invar=no_hospitalizations, timevar=yrsInStudyModified);
%sumdata1(order=8,  invar=no_cardiac_hospitalizations);
%incidence100(order=9, invar=no_cardiac_hospitalizations, timevar=yrsInStudyModified);
%sumdata1(order=10,  invar=count_cancer);
%freqdata1(order=11,  invar=ind_cancer, level=(1), levelname="Cancer - No. of participants");
%freqdata1(order=12,  invar=died, level=(1), levelname="Death - No. of participants");
%sumdata1(order=13,  invar=count_cardiac);
%freqdata1(order=14,  invar=ind_cardiac, level=(1), levelname="Cardiac disorder - No. of
participants");
%sumdata1(order=15,  invar=count_gastro);
%freqdata1(order=16,  invar=ind_gastro, level=(1), levelname="Gastrointestinal disorder - No. of
participants");
%sumdata1(order=17,  invar=count_abdominalPain);
%freqdata1(order=18,  invar=ind_abdominalPain, level=(1), levelname="Abdominal pain - No. of
participants");
%sumdata1(order=19,  invar=count_nervous);
%freqdata1(order=20,  invar=ind_nervous, level=(1), levelname="Nervous system disorder - No. of
participants");
%sumdata1(order=21,  invar=count_renal);
%freqdata1(order=22,  invar=ind_renal, level=(1), levelname="Renal or urinary system disorder -
No. of participants");
%sumdata1(order=23,  invar=count_renalColic);
%freqdata1(order=24,  invar=ind_renalColic, level=(1), levelname="Nephrolithiasis or renal colic
- No. of participants");

%mend datachunk2;


*************************************************************************;
*  Create dataset with all necessary data fields for Study A tables 1 and 2  *;
*************************************************************************;
data baseline;
  set inlib.halt_baseline;
  if study_t = 1;         *study A;

  if (racea=1 or raceb=1 or racec=1 or racef=1) then race_other=1;
  else race_other=0;

  if (racea=0 and raceb=0 and racec=0 and raced=0 and racee=0 and racef=0 and raceg=0) then
race_missing=1;
  else race_missing=0;

  format _all_;
run;

proc freq data = baseline;
  table study randtype  / list missing;
run;

proc sort data = baseline;
  by haltid;
run;

*********************************;
*  This file needs v9.3 or later *;
*********************************;
data genotype(keep=haltid genetype);
 set informs.genetype09022014;
run;

proc sort data=genotype;
  by haltid;
run;

data safety;
  set informs.safety;
  count_cancer = count_nonmelskincancer + count_melanoma + count_othercancer;
  ind_cancer = ind_nonmelskincancer + ind_melanoma + ind_othercancer;
```

```
run;

data table1;
  merge baseline(in=inbase) genotype(in=ing) safety(in=ins);
  by haltid;
  if inbase;
  rename genetype=genotype;
run;

proc freq data = table1(where=(genotype ne .));
  table study*genotype randtype*genotype  ;
run;

*****************************************************************************;
*  Create Study A Table 1                                                   *;
*****************************************************************************;
%let caser=randtype;
*** Column processing;

data accumfreq1 accummean1 accummedian1 accumsum1 accumincid1 accuminert1;
  set _null_;

%datachunk();

data accumtab1;
  set accumfreq1 accummean1 accummedian1 accumsum1 accumincid1 accuminert1;
  if &caser=. then delete;

proc sort data=accumtab1;
  by &caser orderer;

proc print data=accumtab1 noobs;
  by &caser;
  pageby &caser;
  title3 'Table 1 stats for Study Grouping (Treatment vs Control)';
  where &caser in (1 2);

*********************************************************************;
%let caser=study;
*** Column processing;

data accumfreq1 accummean1 accummedian1 accumsum1 accumincid1 accuminert1;
  set _null_;

%datachunk();

data accumtab1;
  set accumfreq1 accummean1 accummedian1 accumsum1 accumincid1 accuminert1;
  if &caser=. then delete;

proc sort data=accumtab1;
  by &caser orderer;

proc print data=accumtab1 noobs;
  by &caser;
  pageby &caser;
  title3 'Table 1 stats for Study Grouping (Blood Pressure)';
  where &caser in (1 2);

*****************************************************************************;
*  Create Study A Table 2                                                   *;
*****************************************************************************;
%let caser=randtype;
*** Column processing;

data accumfreq1 accummean1 accummedian1 accumsum1 accumincid1 accuminert1;
  set _null_;

%datachunk2();
```

```
data accumtab1;
  set accumfreq1 accummean1 accummedian1 accumsum1 accumincid1 accuminert1;
  if &caser=. then delete;

proc sort data=accumtab1;
  by &caser orderer;

proc print data=accumtab1 noobs;
  by &caser;
  pageby &caser;
  title3 'Table 2 stats for Study Grouping (Treatment vs Control)';
  where &caser in (1 2);

*****************************************************************;
%let caser=study;
*** Column processing;

data accumfreq1 accummean1 accummedian1 accumsum1 accumincid1 accuminert1;
  set _null_;

%datachunk2();

data accumtab1;
  set accumfreq1 accummean1 accummedian1 accumsum1 accumincid1 accuminert1;
  if &caser=. then delete;

proc sort data=accumtab1;
  by &caser orderer;

proc print data=accumtab1 noobs;
  by &caser;
  pageby &caser;
  title3 'Table 2 stats for Study Grouping (Blood Pressure)';
  where &caser in (1 2);
```

Appendix B – SAS code for Study B Integrity Check

```
%let flnm = %sysfunc(getoption(sysin));
title "Program saved as: &FLNM.";
title2 "Check HALT_PKD Study B input files for DSIC";

/*****************************************************************************************************
*******************************
Programmer: Patty Griffin
Date: March 26, 2015

Function/Notes: Check HALT_PKD Study B input files for DSIC

Run with SAS v9.3 or later.

*****************************************************************************************************
*******************************/
*  Input file  *;
****************;
libname inlib   "/prj/niddk/ims_analysis/HALT_PKD/private_orig_data/NIDDK/Study Data/Primary
Paper Analysis Data/Final SAS datasets/";
libname informs "/prj/niddk/ims_analysis/HALT_PKD/private_orig_data/NIDDK/Study Data/Non-CRF
Data/";
options nofmterr;

*************;
*  Formats  *;
*************;
proc format;


***********;
*  Macro  *;
***********;

%global caser;


*** Macro ***;
%macro freqdata1(order=, invar=, level=, levelname= );

data data0 data1;
  set _null_;

  proc freq data=table1 noprint;
    tables &invar*&caser/out=data0 outpct missing;
        format _all_;
        run;

data data1;
  set data0;
  length LEVEL $100 LEVELNAME $100;
  LEVEL=strip(&invar);
  LEVELNAME=strip(&levelname);

  data data1(keep=&caser name LEVEL LEVELNAME CHARALL ORDERER);
    set data1;
    length name $100 CHARALL $100;
    name=upcase("&invar");
    PCT_DISP=round(PCT_COL,.1);
    CHARALL=compress(put(COUNT,8.))||" ("||compress(put(PCT_DISP,8.1))||")";
    ORDERER=&order;
    if level in &level then output data1;

data accumfreq1;
  set accumfreq1 data1;

%mend freqdata1;
```

```
%macro meandata1(order=, invar=, roundvar=, digit=);
proc means data=table1 mean stddev  noprint;
        var &invar;
        class &caser;
        output out=data1 mean=mean stddev=stddev ;
        run;

data data1(drop=_TYPE_ _FREQ_ mean stddev );
  set data1;
  length name CHARALL $100;
  name=upcase("&invar");
  mean=round(mean,&roundvar);
  stddev=round(stddev,&roundvar);
  CHARALL=compress(put(mean,8.&digit))||" ± "||compress(put(stddev,8.&digit));
  ORDERER=&order;
  output;

data accummean1;
  set accummean1 data1;

%mend meandata1;

%macro mediandata1(order=, invar=, roundvar=, digit=);
proc means data=table1 median p25 p75 min max noprint;
        var &invar;
        class &caser;
        output out=data1 median=median p25=p25 p75=p75 min=min max=max;
        run;

data data1(drop=_TYPE_ _FREQ_ median p25 p75 min max);
  set data1;
  length name CHARALL $100;
  name=upcase("&invar");
  median=round(median,&roundvar);
  min=round(min,&roundvar);
  max=round(max,&roundvar);
  ORDERER=&order;
  CHARALL=compress(put(median,8.&digit));
  output;
  ORDERER=ORDERER+.01;
  *CHARALL=compress(put(min,8.&digit)||"-"||put(max,8.&digit));
  CHARALL=compress(put(p25,8.&digit)||","||put(p75,8.&digit));
  output;

data accummedian1;
  set accummedian1 data1;

%mend mediandata1;

%macro sumdata1(order=, invar=);
proc means data=table1 sum  noprint;
        var &invar;
        class &caser;
        output out=data1 sum=sum ;
        run;

data data1(drop=_TYPE_ _FREQ_ sum );
  set data1;
  length name CHARALL $100;
  name=upcase("&invar");
  CHARALL=compress(put(sum, 8.));
  ORDERER=&order;
  output;

data accumsum1;
  set accumsum1 data1;

%mend sumdata1;
```

```
%macro inertdata1(order=);
data inert1;
  length orderer &caser 8.;
  orderer=&order.;
  &caser=-1;
  output;
  orderer=&order.;
  &caser=0;
  output;
  orderer=&order.;
  &caser=1;
  output;

data accuminert1;
  set accuminert1 inert1;

%mend inertdata1;


%macro datachunk();

%meandata1(order=1, invar=age, roundvar=.1, digit=1);
%freqdata1(order=2, invar=sex, level=(1), levelname="Male");
%freqdata1(order=3, invar=racee, level=(1), levelname="Race - White");
%freqdata1(order=4, invar=raced, level=(1), levelname="Race - Black");
%freqdata1(order=5, invar=race_other, level=(1), levelname="Race - Other");
%meandata1(order=10, invar=bmi, roundvar=.1, digit=1);
%meandata1(order=11, invar=serumCreat_avg, roundvar=.1, digit=1);
%meandata1(order=12, invar=ckd_epi_egfr, roundvar=.1, digit=1);
%meandata1(order=13, invar=usodium, roundvar=.1, digit=1);
%meandata1(order=14, invar=ualdos, roundvar=.1, digit=1);
%mediandata1(order=15, invar=ualbum, roundvar=.1, digit=1);

%mend datachunk;

%macro datachunk2();

%meandata1(order=1, invar=yrsInStudyModified, roundvar=.1, digit=1);
%freqdata1(order=2, invar=died, level=(1), levelname="Death - No. of participants");
%sumdata1(order=3,  invar=count_cardiac);
%freqdata1(order=4, invar=ind_cardiac, level=(1), levelname="Cardiac disorder - No. of
participants");
%sumdata1(order=5,  invar=count_coronaryArteryDisease);
%freqdata1(order=6, invar=ind_coronaryArteryDisease, level=(1), levelname="Coronary artery
disease - No. of participants");
%sumdata1(order=7,  invar=count_arrhythmias);
%freqdata1(order=8, invar=ind_arrhythmias, level=(1), levelname="Arrhythmia - No. of
participants");
%sumdata1(order=9,  invar=count_otherCardiacDisorder);
%freqdata1(order=10,invar=ind_otherCardiacDisorder, level=(1), levelname="Other - No. of
participants");
%sumdata1(order=11, invar=count_gastro);
%freqdata1(order=12, invar=ind_gastro, level=(1), levelname="Gastrointestinal disorder - No. of
participants");
%sumdata1(order=13, invar=count_nervous);
%freqdata1(order=14,invar=ind_nervous, level=(1), levelname="Nervous system disorder - No. of
participants");
%sumdata1(order=15, invar=count_cerebrovascular);
%freqdata1(order=16,invar=ind_cerebrovascular, level=(1), levelname="Cerebrovascular event - No.
of participants");
%sumdata1(order=18, invar=count_headache);
%freqdata1(order=19,invar=ind_headache, level=(1), levelname="Headache - No. of participants");
%sumdata1(order=20, invar=count_otherNervous);
%freqdata1(order=21,invar=ind_otherNervous, level=(1), levelname="Other - No. of participants");
%sumdata1(order=22,  invar=count_renal);
%freqdata1(order=23,  invar=ind_renal, level=(1), levelname="Renal or urinary system disorder -
No. of participants");
%sumdata1(order=24,  invar=count_renalHemorrhage);
```

```
%freqdata1(order=25,  invar=ind_renalHemorrhage, level=(1), levelname="Renal hemorrhage or
hematuria - No. of participants");
%sumdata1(order=26,  invar=count_renalColic);
%freqdata1(order=27,  invar=ind_renalColic, level=(1), levelname="Nephrolithiasis or renal colic
- No. of participants");
%sumdata1(order=28,  invar=count_acuteKidneyInjury);
%freqdata1(order=29,  invar=ind_acuteKidneyInjury, level=(1), levelname="Acute kidney injury -
No. of participants");
%sumdata1(order=30,  invar=count_otherRenal);
%freqdata1(order=31,  invar=ind_otherRenal, level=(1), levelname="Other - No. of participants");

%mend datachunk2;

*******************************************************;
*  Create the report for all of the datasets in inlib  *;
*******************************************************;
data baseline;
  set inlib.halt_baseline;
  if study_t = 2;         *study B;

  if (racea=1 or raceb=1 or racec=1 or racef=1) then race_other=1;
  else race_other=0;

  format _all_;
run;

proc freq data = baseline;
  table study randtype  / list missing;
run;

proc sort data = baseline;
  by haltid;
run;

*********************************;
*  This file needs v9.3 or later *;
*********************************;
data genotype(keep=haltid genetype);
 set informs.genetype09022014;
run;

proc sort data=genotype;
  by haltid;
run;

data safety;
  set informs.safety;
  count_otherNervous = count_otherNervousSystemDisorder + count_syncope  ;  *defined in
PrimaryPaper_StudyB.sas program;
  ind_otherNervous = ind_otherNervousSystemDisorder + ind_syncope  ;
  count_otherRenal = count_otherRenalSystemDisorder + count_urinaryTractObstruct; *defined in
PrimaryPaper_StudyB.sas program;
  ind_otherRenal = ind_otherRenalSystemDisorder + ind_urinaryTractObstruct;
run;

data table1;
  merge baseline(in=inbase) genotype(in=ing) safety(in=ins);
  by haltid;
  if inbase;
  rename genetype=genotype;
run;

proc freq data = table1(where=(genotype ne .));
  table study*genotype randtype*genotype ;
run;

proc freq data = table1;
  table randtype*racea*raceb*racec*raced*racee*racef*raceg / list missing;
run;
```

```
*************************************************************************;
*  Create Study B Table 1                                               *;
*************************************************************************;
%let caser=randtype;
*** Column processing;

data accumfreq1 accummean1 accummedian1 accumsum1 accuminert1;
  set _null_;

%datachunk();

data accumtab1;
  set accumfreq1 accummean1 accummedian1 accumsum1 accuminert1;
  if &caser=. then delete;

proc sort data=accumtab1;
  by &caser orderer;

proc print data=accumtab1 noobs;
  by &caser;
  pageby &caser;
  title3 'Table 1 stats for Study Grouping (Treatment vs Control)';
  where &caser in (1 2);
run;

*************************************************************************;
*  Create Study B Table 2                                               *;
*************************************************************************;
data accumfreq1 accummean1 accummedian1 accumsum1 accumincid1 accuminert1;
  set _null_;

%datachunk2();

data accumtab1;
  set accumfreq1 accummean1 accummedian1 accumsum1 accumincid1 accuminert1;
  if &caser=. then delete;

proc sort data=accumtab1;
  by &caser orderer;

proc print data=accumtab1 noobs;
  by &caser;
  pageby &caser;
  title3 'Table 2 stats for Study Grouping (Treatment vs Control)';
  where &caser in (1 2);

**** Endpoints DSIC;
title 'HALT-PKD Endpoints DSIC';

title2 ' ';



libname haltpkd '/prj/niddk/ims_analysis/HALT_PKD/private_orig_data/';

libname analysis '/prj/niddk/ims_analysis/HALT_PKD/private_orig_data/NIDDK/Study Data/Primary
Paper Analysis Data/Final SAS datasets/';

libname out
'/prj/niddk/dataset_files/HALT_PKD_V3/Data/Primary_Paper_Analysis_Data/Final_SAS_datasets/';



%include '/prj/niddk/ims_analysis/HALT_PKD/private_orig_data/NIDDK/Study Data/Primary Paper
Analysis Data/Final SAS programs/HALT_format.sas';
```

```
options nofmterr;


data endpoints;
        set haltpkd.endpoints_sep2014;


data out.endpoints_sep2014;
        set endpoints;


proc contents data = endpoints;


data studyb;
 set endpoints;
 by haltid;
if study_t=2;
if esrd = 1 or egfr_50 = 1 or death = 1 then composite_outcome = 1;
else composite_outcome = 0;
if b2date='09SEP1900'd then b2date=.;
*DAYS from b2Date;
**any endpoint;
if any_endpoint_date ne . then days_anyEnd = (any_endpoint_date-b2Date);
 else days_anyEnd = (lastVisit_rev-b2Date);
**death;
if dthdate ne . then days_death = (dthdate-b2Date);
 else days_death = (lastVisit_rev-b2Date);
**ESRD;
if tosdate ne . then days_esrd = (tosdate-b2Date);
 else days_esrd = (lastVisit_rev-b2Date);
**50% reduction eGFR;
**note: confsdate is confirmation sample date;
if confsdate ne . then days_egfr50 = (confsdate-b2Date);
 else days_egfr50 = (lastVisit_rev-b2Date);
*YEARS from b2Date;
yrsToAnyEnd = round(days_anyEnd/365.25);
```

```
yrsToDeath  = round(days_death/365.25);
yrsToESRD = round(days_esrd/365.25);
yrsToEGFR50 = round(days_egfr50/365.25);
format randtype randtype2f.;
run;


proc freq data = studyb;
        tables  death*randtype esrd*randtype egfr_50*randtype composite_outcome*randtype /list
missing;
        format randtype randtype2f.;


proc phreg data = studyb;
        class randtype (ref = 'Lisinopril/Telmisartan');
        model yrsToAnyEnd*composite_outcome(0) = randtype age sex  /risklimits ties=efron;
        strata siteid;


proc phreg data = studyb;
        class randtype (ref = 'Lisinopril/Placebo') ;
        model yrsToDeath * death(0) = randtype age sex ckd_epi_eGFR0 /risklimits ties=efron;
        strata siteid;
        baseline out=survs survival=s;


proc phreg data = studyb;
        class randtype (ref = 'Lisinopril/Placebo') ;
        model yrsToESRD*esrd(0)= randtype age sex ckd_epi_eGFR0 /risklimits ties=efron;
        strata siteid;
        baseline out=survs survival=s;


proc phreg data = studyb;
        class randtype (ref = 'Lisinopril/Telmisartan');
        model yrsToEGFR50*egfr_50(0) = randtype age sex ckd_epi_eGFR0 /risklimits ties=efron;
        strata siteid;
        baseline out=survs survival=s;
```

```
ods graphics on;

ods path show;
ods path(prepend) work.templat(update);

proc template;
define style MYSTYLE4;
parent=STYLES.MYSTYLE;
 style GraphFonts from GraphFonts
         "Fonts used in graph styles" /
         'GraphDataFont'  = ("<sans-serif>, <MTsans-serif>",9pt,bold)
         'GraphValueFont' = ("<sans-serif>, <MTsans-serif>",9pt,bold)
         'GraphLabelFont' = ("<sans-serif>, <MTsans-serif>",9pt,bold)
                'GraphValueText' = ("<sans-serif>, <MTsans-serif>",9pt,bold);
 style GraphData1 from GraphData1/linestyle=1 contrastcolor=blue markersymbol='circlefilled';
 style GraphData2 from GraphData2/linestyle=2 contrastcolor=red  markersymbol='circle';
end;
run;


ods listing style=mystyle4;

%macro life (title=,var1=,var2=);

proc template;
   define statgraph Stat.Lifetest.Graphics.ProductLimitSurvival;
      dynamic NStrata xName plotAtRisk plotCensored plotCL plotHW plotEP
         labelCL labelHW labelEP maxTime xtickVals xtickValFitPol method
         StratumID classAtRisk plotBand plotTest GroupName yMin /*Transparency*/
         SecondTitle TestName pValue;
      BeginGraph;
        if (NSTRATA=1)
/*
```

```
            if (EXISTS(STRATUMID))
               entrytitle  " " " for " STRATUMID;
            else
               entrytitle  " " "";
            endif;
            if (PLOTATRISK)
               entrytitle "" / textattrs=
                  GRAPHVALUETEXT;
            endif;
*/


            layout overlay / xaxisopts=(label="Survival Time (Years)" shortlabel=XNAME
offsetmin=.05
               linearopts=(viewmax=MAXTIME tickvaluelist=XTICKVALS
               tickvaluefitpolicy=XTICKVALFITPOL)) yaxisopts=(label=
               "&title" shortlabel="Survival" linearopts=(
               viewmin=0 viewmax=1 tickvaluelist=(0 .2 .4 .6 .8 1.0)));
               if (PLOTHW=1 AND PLOTEP=0)
                  bandplot LimitUpper=HW_UCL LimitLower=HW_LCL x=TIME /
                     modelname="Survival" fillattrs=GRAPHCONFIDENCE name="HW"
                     legendlabel=LABELHW;
               endif;
               if (PLOTHW=0 AND PLOTEP=1)
                  bandplot LimitUpper=EP_UCL LimitLower=EP_LCL x=TIME /
                     modelname="Survival" fillattrs=GRAPHCONFIDENCE name="EP"
                     legendlabel=LABELEP;
               endif;
               if (PLOTHW=1 AND PLOTEP=1)
                  bandplot LimitUpper=HW_UCL LimitLower=HW_LCL x=TIME /
                     modelname="Survival" fillattrs=GRAPHDATA1
                     /*datatransparency=.55*/ name="HW" legendlabel=LABELHW;
                  bandplot LimitUpper=EP_UCL LimitLower=EP_LCL x=TIME /
                     modelname="Survival" fillattrs=GRAPHDATA2
                     /*datatransparency=.55*/ name="EP" legendlabel=LABELEP;
```

```
            endif;
            if (PLOTCL=1)
               if (PLOTHW=1 OR PLOTEP=1)
                  bandplot LimitUpper=SDF_UCL LimitLower=SDF_LCL x=TIME /
                     modelname="Survival" display=(outline) outlineattrs=
                     GRAPHPREDICTIONLIMITS name="CL" legendlabel=LABELCL;
               else
                  bandplot LimitUpper=SDF_UCL LimitLower=SDF_LCL x=TIME /
                     modelname="Survival" fillattrs=GRAPHCONFIDENCE name=
                     "CL" legendlabel=LABELCL;
               endif;
            endif;
            stepplot y=SURVIVAL x=TIME / name="Survival" rolename=(_tip1=
               ATRISK _tip2=EVENT) tip=(y x Time _tip1 _tip2) legendlabel=
               "Survival" lineattrs=(thickness=2.5);
            if (PLOTCENSORED=1)
               scatterplot y=CENSORED x=TIME / markerattrs=(symbol=plus)
                  name="Survival" legendlabel="Censored";
            endif;
            if (PLOTCL=1 OR PLOTHW=1 OR PLOTEP=1)
               discretelegend "Censored" "CL" "HW" "EP" / location=outside
                  halign=center;
           /* else
               if (PLOTCENSORED=1)
                  discretelegend "Censored" / location=inside valign=bottom haligh=center
*autoalign=(bottom
                     topright bottomleft)*;
               endif;*/
            endif;
            if (PLOTATRISK=1)
               innermargin / align=bottom;
                  blockplot x=TATRISK block=ATRISK / repeatedvalues=true
                     display=(values) valuehalign=start valuefitpolicy=
                     truncate labelposition=left /*labelattrs=GRAPHVALUETEXT
```

```
                        valueattrs=GRAPHDATATEXT (size=9pt)*/
                        includemissingclass=false;
                  endinnermargin;
               endif;
            endlayout;
         else
/*
            entrytitle METHOD " " " ";
            if (EXISTS(SECONDTITLE))
               entrytitle SECONDTITLE / textattrs=GRAPHVALUETEXT;
            endif;
*/
            layout overlay / xaxisopts=(label="Survival Time (Years)" shortlabel=XNAME
offsetmin=.05
               linearopts=(viewmax=MAXTIME tickvaluelist=(0 1 2 3 4 5 6 7 8)
               tickvaluefitpolicy=XTICKVALFITPOL)) yaxisopts=(label=
               "&title" shortlabel="Survival" linearopts=(
               viewmin=0 viewmax=1 tickvaluelist=(0 .2 .4 .6 .8 1.0)));
               if (PLOTHW)
                  bandplot LimitUpper=HW_UCL LimitLower=HW_LCL x=TIME / group=
                     STRATUM index=STRATUMNUM modelname="Survival"
                     /*datatransparency=Transparency*/;
               endif;
               if (PLOTEP)
                  bandplot LimitUpper=EP_UCL LimitLower=EP_LCL x=TIME / group=
                     STRATUM index=STRATUMNUM modelname="Survival"
                     /*datatransparency=Transparency*/;
               endif;
               if (PLOTCL)
                  if (PLOTBAND)
                     bandplot LimitUpper=SDF_UCL LimitLower=SDF_LCL x=TIME /
                        group=STRATUM index=STRATUMNUM modelname="Survival"
                        display=(outline);
                  else
```

```
            bandplot LimitUpper=SDF_UCL LimitLower=SDF_LCL x=TIME /
               group=STRATUM index=STRATUMNUM modelname="Survival"
               /*datatransparency=Transparency*/;
         endif;
      endif;
      stepplot y=SURVIVAL x=TIME / group=STRATUM index=STRATUMNUM
         name="Survival" rolename=(_tip1=ATRISK _tip2=EVENT) tip=(y x
         Time _tip1 _tip2) lineattrs=(thickness=3px);
      if (PLOTCENSORED)
         scatterplot y=CENSORED x=TIME / group=STRATUM index=
            STRATUMNUM markerattrs=(symbol=plus);
      endif;
      if (PLOTATRISK)
         innermargin / align=bottom;
            blockplot x=TATRISK block=ATRISK / class=CLASSATRISK
               repeatedvalues=true display=(label values) valuehalign
               =start valuefitpolicy=truncate labelposition=left
               /*labelattrs=GRAPHVALUETEXT /*valueattrs=GRAPHDATATEXT (
               size=9pt)*/ includemissingclass=false;
         endinnermargin;
      endif;
      /*DiscreteLegend "Survival" / title="" location=inside valign=bottom
halign=center;*/
      if (PLOTCENSORED)
         if (PLOTTEST)
            layout gridded / rows=2 /*autoalign=(BOTTOM TOPRIGHT BOTTOMLEFT
               TOP)*/ border=false BackgroundColor=
               GraphWalls:Color Opaque=true;
               entry "";
               if (PVALUE < .0001)
                  entry TESTNAME " p " eval (PUT(PVALUE, PVALUE6.4));
               else
                  entry TESTNAME " p=" eval (PUT(PVALUE, PVALUE6.4));
               endif;
```

```
                  endlayout;
               else
                  layout gridded / rows=1 /*autoalign=(BOTTOM TOPRIGHT BOTTOMLEFT
                     TOP)*/ border=false BackgroundColor=
                     GraphWalls:Color Opaque=true;
                     entry "";
                  endlayout;
               endif;
            else
               if (PLOTTEST)
                  layout gridded / rows=1 /*autoalign=(BOTTOM TOPRIGHT BOTTOMLEFT
                     TOP)*/ border=true BackgroundColor=
                     GraphWalls:Color Opaque=true;
                     if (PVALUE < .0001)
                        entry TESTNAME " p " eval (PUT(PVALUE, PVALUE6.4));
                     else
                        entry TESTNAME " p=" eval (PUT(PVALUE, PVALUE6.4));
                     endif;
                  endlayout;
               endif;
            endif;
         endlayout;
      endif;
   EndGraph;
end;
run;


proc lifetest data = studyb notable plots = survival(atrisk=0 to 8 by 1 nocensor);
time &var1 * &var2(0);
strata randtype;
test randtype;
run;
```

```
%mend;



%life(title=Event Free Survival (Composite Endpoint),var1=yrsToAnyEnd,var2=any_endpoint);

%life(title=Event Free Survival (Death),var1=yrsToDeath,var2=death);

%life(title=Event Free Survival (End Stage Renal Disease),var1=yrsToESRD,var2=esrd);

%life(title=Event Free Survival (50% reduction eGFR),var1=yrsToEGFR50,var2=egfr_50);
```