Digitalis Investigation Group (DIG)
Data Documentation

The DIG Trial was a randomized, double-blind, multicenter trial with more than 300 centers in the United States and Canada participating. The purpose of the trial was to examine the safety and efficacy of Digoxin in treating patients with congestive heart failure in sinus rhythm. Digitalis was introduced clinically more than 200 years ago and has since become a commonly prescribed medication for the treatment of heart failure; however, there was considerable uncertainty surrounding its safety and efficacy. Small trials indicated that Digoxin alleviated some of the symptoms of heart failure, prolonged exercise tolerance, and generally improved the quality of patients' lives. Unfortunately, these trials were generally small and although they did focus on the effect of treatment on patients' relief from heart failure symptoms and quality of life, they failed to address the effect of treatment on cardiovascular outcomes. Questions about the safety of Digoxin were also a concern. Digoxin toxicity is uncommon in small trials with careful surveillance, however, the long-term effects of therapeutic levels of Digoxin were less clear.

The DIG dataset consists of baseline and outcome data from the main DIG trial. In the main trial, heart failure patients meeting the eligibility criterion and whose ejection fraction was 45% or less were randomized to receive either a placebo or digoxin. Outcomes assessed in the trial included: cardiovascular mortality, hospitalization or death from worsening heart failure, hospitalization due to other cardiovascular causes and hospitalization due to non-cardiovascular causes.

The dataset was prepared to enable students to reproduce the analysis leading to the results of the paper published in the New England Journal of Medicine in 1997 (*The effect of digoxin on mortality and morbidity in patients with heart failure*. The Digitalis Investigation Group. N Engl J Med. 1997 Feb 20;336(8):525-33) by the Digitalis Investigation Group. Some data not discussed in the NEJM article are included in the teaching data set (body mass index, serum creatinine, serum potassium, systolic and diastolic blood pressure, etc.). In order to create an anonymous dataset that protects patient confidentiality, most variables have been permuted over the set of patients within treatment group. Therefore, **this dataset can reproduce the results of the NEJM paper; however, it would be inappropriate to use this dataset for other research or publication purposes.** Multidimensional relationships, not included in the NEJM, may not have been preserved during the permutation process.

The remainder of the documentation includes baseline and event forms, annotated with variable names, output from SAS contents procedure and selected means and proportions from the DIG dataset.

NHLBI-VA Study #995
Revised FEB 1992

DIGITALIS INVESTIGATION GROUP

BASELINE FORM

Local Center Name _____

Randomization Number
_____/_____
__ __ __ / __ __ __ __

PRINT Patient Name _____ ID _____
Last First M.I.

Date of Randomization Mo __ __ Day __ __ Yr __ __

Items 1 through 9 must be transmitted over the telephone at the time of randomization.

1. SOCIAL SECURITY NUMBER ..... __ __ __ - __ __ - __ __ __ __
2. DATE OF BIRTH ..... Mo Day Yr
3. EJECTION FRACTION (percent) ..... EJF_PER

   A. METHOD (1=Radionuclide, 2=Angiography, 3=2-D Echo) ..... EJFMETH
4. SEX (1=Male, 2=Female) ..... SEX
5. RACE (1=White, 2=Nonwhite) ..... RACE
6. CHEST X-RAY (CT-ratio) ..... CHESTX
7. WEIGHT ..... Kg OR lbs.
8. HEIGHT ..... cms OR inches
9. SERUM CREATININE LEVEL ..... CREAT mg/dl OR μ mol/l

9A. SERUM POTASSIUM LEVEL ..... KLEVEL mEq/l OR __.__ mmol/l

10. PLEASE RECORD RECOMMENDED DIGOXIN DOSE ..... DIGDOSER
11. PLEASE RECORD RANDOMIZATION NUMBER .....

Complete the following information - <u>not</u> to be transmitted by telephone.

12. APPROXIMATE DURATION OF CHF (months) ..... CHFDUR

<u>SIGNS OR SYMPTOMS</u>: 0=None or Unknown, 1=Present, 2=Past, 3=Present and Past
(Present is defined as <u>≤</u> 1 month. Past is > 1 month prior to randomization.)

13. RALES ..... RALES
14. ELEVATED JUGULAR VENOUS PRESSURE ..... ELEVJVP
15. PERIPHERAL EDEMA ..... PEDEMA
16. DYSPNEA AT REST OR ORTHOPNEA ..... RESTDYS
17. DYSPNEA ON EXERTION ..... EXERTDYS
18. LIMITATION OF ACTIVITY ..... ACTLIMIT
19. S_3 ..... S3
20. RADIOLOGIC EVIDENCE OF PULMONARY CONGESTION ..... PULCONG
21. HEART RATE (beats/minute) ..... HEARTRTE
22. BLOOD PRESSURE (mm Hg) ..... SYSBP / DIABP
23. CURRENT NYHA FUNCTIONAL CLASS (use codes below) ..... FUNCTCLS

    1 = Class I (Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue or dyspnea).
    2 = Class II (Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes fatigue or dyspnea).
    3 = Class III (Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue or dyspnea).
    4 = Class IV ((Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency are present even at rest. If any physical activity is undertaken, symptoms are increased.)

STUDY #995 - BASELINE FORM (PAGE 2 OF 2) RANDOMIZATION NO. __ __ __ / __ __ __ __

24. ETIOLOGY OF CHF ..... PRIMARY CHFETIOL
    1=Ischemic 4=Idiopathic
    2=Hypertensive 5=Alcohol related
    3=Valvular 6=Other
    Specify _____

CODE: YES = 1
NO OR UNKNOWN = 0

25. PREVIOUS MYOCARDIAL INFARCTION ..... PREVMI
26. CURRENT ANGINA ..... ANGINA
27. HISTORY OF DIABETES ..... DIABETES
28. HISTORY OF HYPERTENSION ..... HYPERTEN

CURRENT DRUG USE:

29. USE OF DIGOXIN WITHIN ONE WEEK PRIOR TO RANDOMIZATION ..... DIGUSE
30. POTASSIUM-SPARING DIURETICS ..... DIURETK
31. OTHER DIURETICS ..... DIURET
31A. POTASSIUM SUPPLEMENT ..... KSUPP
32. ACE INHIBITOR ..... ACEINHIB
33. NITRATES (ORAL OR PASTE) ..... NITRATES
34. HYDRALAZINE ..... HYDRAL
35. OTHER VASODILATORS, SPECIFY ..... VASOD
36. DOSE OF DIGOXIN/PLACEBO (D-995) PRESCRIBED (mg/day) ..... DIGDOSE
    (For all doses, give the patient one bottle of study drug.)
37. PATIENT ADDRESS: _____
    TELEPHONE: AREA CODE: _____ NUMBER: _____
38. NAME, ADDRESS AND TELEPHONE NO. OF FAMILY OR PRIVATE PHYSICIAN:
    NAME: _____
    ADDRESS: _____
    TELEPHONE: AREA CODE: _____ NUMBER: _____
39. NAME, ADDRESS AND TELEPHONE NO. OF CLOSE FRIEND OR RELATIVE NOT LIVING WITH PATIENT:
    NAME: _____
    ADDRESS: _____
    TELEPHONE: AREA CODE: _____ NUMBER: _____
40. DATE OF NEXT VISIT ..... Mo __ __ Day __ __ Yr __ __
41. LAST NAME AND FIRST INITIAL OF INDIVIDUAL RANDOMIZING PATIENT (IN CAPITALS) ..... _____
    Last First Initial

Signature _____

PLEASE RETURN FORM TO DATA COORDINATING CENTER AT PERRY POINT.

Calculated variables:

AGE (in years): INT(Date of Randomization-Date of Birth)/365.25

BMI (Body Mass Index): Weight in kg/Height in meters^2

NSYM (Number of symptoms of CHF): Sum of Questions 13 through 20. If sign or symptom of CHF was either currently or previously present, then symptom was considered ‘present’. The sum of all present symptoms was assigned to NSYM. If the sum was four or more, then it was assigned the value 4.

TRTMT (Placebo or active treatment assignment): 0=Assigned to placebo group, 1=Assigned to treatment group

DIGITALIS INVESTIGATION GROUP

EVENT FORM

Local Center Name _____

PRINT Patient Name _____
Last First M.I.

Randomization Number
_____/_____
__ __ __ __ __ __ __

Date of Event Mo __ __ Day __ __ Yr __ __

PLEASE COMPLETE A SEPARATE EVENT FORM FOR EACH HOSPITALIZATION OR EPISODE OF SUSPECTED DIGOXIN TOXICITY. CODE DISCHARGE DIAGNOSES FOR EACH HOSPITALIZATION.

A. HOSPITALIZATION (Defined as admission to hospital for at least 24 hours.)

		CODE: 1=YES 0=NO	Days Rand To Event (1)
01.	WAS PATIENT HOSPITALIZED? (If No, Go to Section B) ..... IF YES, COMPLETE QUESTIONS 02 THROUGH 17 AND QUESTIONS 27a AND 27b.		
02.	WORSENING HEART FAILURE	WHF	WHFDAYS
03.	DIGOXIN TOXICITY (If YES, complete Section B below)	DIG	DIGDAYS
04.	MYOCARDIAL INFARCTION	MI	MIDAYS
05.	UNSTABLE ANGINA	UANG	UANGDAYS
06.	STROKE	STRK	STRKDAYS
07.	ARRHYTHMIA - SUPRAVENTRICULAR	SVA	SVADAYS
08.	ARRHYTHMIA - VENTRICULAR	VENA	VENADAYS
09*.	CORONARY ARTERY BYPASS GRAFT SURGERY (CABG)	CREV	CREVDAYS
10*.	PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY (PTCA)	CREV	CREVDAYS
11.	CARDIAC TRANSPLANTATION		
12.	VALVE OPERATION		
&13.	OTHER CARDIAC SURGERY, SPECIFY _____	OCVD	OCVDDAYS
&14.	OTHER CARDIOVASCULAR REASON, SPECIFY _____	OCVD	OCVDDAYS
15.	RESPIRATORY INFECTION	RINF	RINFDAYS
16.	OTHER NONCARDIAC, NONVASCULAR REASON, SPECIFY _____	OTH	OTHDAYS
17.	ENTER NUMBER OF PRIMARY REASON FOR HOSPITALIZATION (USE QUESTIONS 02-16 TO CODE)		

* CABG and PTCA surgeries combined to create the composite variable Coronary Revascularization (CREV)

&Other cardiac surgery and Other cardiovascular reason combined to form composite variable Other CVD (OCVD).

(1) If no event occurred, number of days is from randomization until l date of last contact or date of death

Derived Variables or events not included on the Event Form:

CVD (CVD Hospitalization): First Hospitalization for CVD cause (Worsening heart failure, Arrythmia, Digoxin Toxicity, MI, Unstable angina, Stroke, Coronary revascularization, Cardiac transplantation, other cardiovascular)

CVDDAYS (Days randomization to first CVD Hosp.): Number of days from randomization to the first hospitalization for a CVD cause.

HOSP (First Hospitalization for any reason): First Hospitalization for patient

HOSPDAYS (Days randomization to first Hospitalization): Number of days from randomization to the first hospitalization.

NHOSP (Number of Hospitalizations): Number of times a patient was hospitalized over the course of the study

NOTE: The Atrioventricular Block, Bradyarrythmia event indicated in the NEJM article was not included with this version of the DIG dataset due to the small number of events. The event 'Unspecified Hospitalization' was combined with Other Non-Cardiac, Non-Vascular Hospitalization and the event 'Cardiac Transplantation' was combined with 'Other Cardiovascular' also due to small counts.

FOLLOW-UP FORM

Local Center Name _____

PRINT Patient Name _____
Last First M.I.

Randomization Number
__ __ __ / __ __ __ __

Date of Follow-Up Visit Mo __ __ Day __ __ Yr __ __

CIRCLE CLOSEST VISIT (MONTH)	01*	04	08	12*	16	20	24	28	32	36	40	44	48	52	56	60
NUMBER:																

(*Please draw Digoxin blood level at this visit if instructed by the Data Coordinating Center.)

1. DID PATIENT DIE ?(0=No, 1=Yes): ..... DEATH

   A. DATE OF DEATH ..... Mo Day Yr

   B. PRIMARY CAUSE OF DEATH ..... REASON
   1=Worsening Heart Failure
   2=Other Cardiac
   3=Other Vascular
   4=Unknown
   5=Non cardiac, nonvascular cause

Derived Variables:

DEATHDAY : Number of days from Randomization till date of death or last contact date if alive

DWHF: Primary study endpoint: Death or Hospitalization from worsening heart failure.

DWHFDAYS: Days from randomization to the primary endpoint of death or hospitalization from worsening heart failure.

The CONTENTS Procedure

Data Set Name:	DIG	Observations:	6800
Member Type:	DATA	Variables:	72
Engine:	V612	Indexes:	0
Created:		Observation Length:	576
Last Modified:		Deleted Observations:	0
Protection:		Compressed:	NO
Data Set Type:		Sorted:	NO
Label:			

-----Engine/Host Dependent Information-----

Data Set Page Size:	16384
Number of Data Set Pages:	244
First Data Page:	1
Max Obs per Page:	28
Obs in First Data Page:	12
Number of Data Set Repairs:	0
File Name:	dig.sd2
Release Created:	6.08.00
Host Created:	WIN

The CONTENTS Procedure

-----Variables Ordered by Position-----

#	Variable	Type	Len	Label
1	ID	Num	8	Patient ID
2	TRTMT	Num	8	0=Placebo, 1=Treatment
3	AGE	Num	8	Calculated: age at randomization
4	RACE	Num	8	Q5: Race, 1=White 2=Nonwhite
5	SEX	Num	8	Q4: Sex, 1=Male 2=Female
6	EJF_PER	Num	8	Q3: Ejection fraction (percent)
7	EJFMETH	Num	8	Q3A: Ejection Fraction method
8	CHESTX	Num	8	Q6: Chest X-ray (CT-Ratio)
9	BMI	Num	8	Calculated: Body Mass Index (kg/M*M)
10	KLEVEL	Num	8	Q9A: Serum Potassium level
11	CREAT	Num	8	Q9: Serum Creatinine (mg/dL)
12	DIGDOSER	Num	8	Q10: Recommended Digoxin dose
13	CHFDUR	Num	8	Q12: Duration of CHF (months)
14	RALES	Num	8	Q13: Rales
15	ELEVJVP	Num	8	Q14: Elevated jugular venous pressure
16	PEDEMA	Num	8	Q15: Peripheral Edema
17	RESTDYS	Num	8	Q16: Dyspnea at Rest
18	EXERTDYS	Num	8	Q17: Dyspnea on Exertion
19	ACTLIMIT	Num	8	Q18: Limitation of activity
20	S3	Num	8	Q19: S3 Gallop
21	PULCONG	Num	8	Q20: Pulmonary congestion
22	NSYM	Num	8	Calculated: Sum of Q13-Q20, Y/N status
23	HEARTRTE	Num	8	Q21: Heart Rate (beats/min)
24	DIABP	Num	8	Q22: Diastolic BP (mmHg)
25	SYSBP	Num	8	Q22: Sysolic BP (mmHg)
26	FUNCTCLS	Num	8	Q23: NYHA Functional Class
27	CHFETIOL	Num	8	Q24: CHF Etiology
28	PREVMI	Num	8	Q25: Previous Myocardial Infarction
29	ANGINA	Num	8	Q26: Current Angina
30	DIABETES	Num	8	Q27: History of Diabetes
31	HYPERTEN	Num	8	Q28: History of Hypertension
32	DIGUSE	Num	8	Q29: Digoxin within past week
33	DIURETK	Num	8	Q30: Potassium sparing Diuretics
34	DIURET	Num	8	Q31: Other Diuretics
35	KSUPP	Num	8	Q31A: Potassium supplements
36	ACEINHIB	Num	8	Q32: Ace inhibitors
37	NITRATES	Num	8	Q33: Nitrates
38	HYDRAL	Num	8	Q34: Hydralazine
39	VASOD	Num	8	Q35: Other Vasodilators
40	DIGDOSE	Num	8	Q36: Dose of Digoxin/Placebo prescribed
41	CVD	Num	8	Hosp: Cardiovascular Disease
42	CVDDAYS	Num	8	Days randomization to First CVD Hosp
43	WHF	Num	8	Hosp: Worsening Heart Failure
44	WHFDAYS	Num	8	Days randomization to First WHF Hosp
45	DIG	Num	8	Hosp: Digoxin Toxicity
46	DIGDAYS	Num	8	Days rand. to First Digoxin Tox Hosp
47	MI	Num	8	Hosp: Myocardial Infarction
48	MIDAYS	Num	8	Days randomization to First MI Hosp
49	UANG	Num	8	Hosp: Unstable Angina
50	UANGDAYS	Num	8	Days rand. to First Unstable Angina Hosp
51	STRK	Num	8	Hosp: Stroke
52	STRKDAYS	Num	8	Days randomization to First Stroke Hosp
53	SVA	Num	8	Hosp: Supraventricular Arrhythmia
54	SVADAYS	Num	8	Days rand. to First SupraVent Arr. Hosp
55	VENA	Num	8	Hosp: Ventricular Arrhythmia

The CONTENTS Procedure

-----Variables Ordered by Position-----

#	Variable	Type	Len	Label
56	VENADAYS	Num	8	Days rand. to First Vent. Arr. Hosp
57	CREV	Num	8	Hosp: Coronary Revascularization
58	CREVDAYS	Num	8	Days rand. to First Cor. Revasc.
59	OCVD	Num	8	Hosp: Other Cardiovascular Event
60	OCVDDAYS	Num	8	Days rand. to First Other CVD Hosp
61	RINF	Num	8	Hosp: Respiratory Infection
62	RINFDAYS	Num	8	Days rand. to First Resp. Infection Hosp
63	OTH	Num	8	Hosp: Other noncardiac, nonvascular
64	OTHDAYS	Num	8	Days rand. to 1st Other Non CVD Hosp
65	HOSP	Num	8	Hosp: Any Hospitalization
66	HOSPDAYS	Num	8	Days randomization to First Any Hosp
67	NHOSP	Num	8	Number of Hospitalizations
68	DEATH	Num	8	Vital Status of Patient 1=Death 0=Alive
69	DEATHDAY	Num	8	Days till last followup or death
70	REASON	Num	8	Cause of Death
71	DWHF	Num	8	Primary Endpt: Death or Hosp from HF
72	DWHFDAYS	Num	8	Days rand. to death or Hosp from WHF

DIG Trial: Selected Means by Treatment Group

	Placebo				Digoxin			
	N	Mean	Median	Std	N	Mean	Median	Std
Calculated: age at randomization	3403	63.55	65.0	10.81	3397	63.42	64.0	11.02
Q22: Sysolic BP (mmHg)	3401	126.02	124.0	19.94	3396	125.57	122.0	19.94
Q22: Diastolic BP (mmHg)	3400	74.91	75.0	11.06	3395	74.89	75.0	11.47
Q9: Serum Creatinine (mg/dL)	3403	1.29	1.2	0.37	3397	1.28	1.2	0.37
Q9A: Serum Potassium level	2993	4.46	4.3	7.87	3006	4.33	4.3	0.51
Q6: Chest X-ray (CT-Ratio)	3402	0.53	0.5	0.07	3396	0.53	0.5	0.07
Q12: Duration of CHF (months)	3397	29.80	16.0	36.55	3389	30.52	17.0	37.21
Q3: Ejection fraction (%)	3403	28.45	29.0	8.85	3397	28.63	29.0	8.85

DIG Trial: Selected Proportions by Treatment Group

	Placebo		Digoxin	
	N	ColPctN	N	ColPctN
Q4: Sex, 1=Male 2=Female				
Men	2634	77.6	2631	77.8
Women	760	22.4	752	22.2
Q5: Race, 1=White 2=Nonwhite				
White	2891	85.2	2899	85.7
Non-white	503	14.8	484	14.3
Q23: NYHA Functional Class				
Class I	440	13.0	464	13.7
Class II	1851	54.5	1805	53.4
Class III	1037	30.6	1039	30.7
Class IV	66	1.9	75	2.2
Q25: Previous Myocardial Infarction				
No	1177	34.7	1192	35.2
Yes	2217	65.3	2191	64.8
Q26: Current Angina				
No	2497	73.6	2462	72.8
Yes	897	26.4	921	27.2
Q27: History of Diabetes				
No	2423	71.4	2426	71.7
Yes	971	28.6	957	28.3
Q28: History of Hypertension				
No	1843	54.3	1859	55.0
Yes	1551	45.7	1524	45.0
Q29: Digoxin within past week				
No	1880	55.4	1891	55.9
Yes	1514	44.6	1492	44.1
Q30: Potassium sparing Diuretics				
No	3117	91.8	3145	93.0
Yes	277	8.2	238	7.0
Q31: Other Diuretics				
No	729	21.5	737	21.8
Yes	2665	78.5	2646	78.2
Q32: Ace inhibitors				
No	178	5.2	200	5.9
Yes	3216	94.8	3183	94.1
Q33: Nitrates				
No	1932	56.9	1958	57.9
Yes	1462	43.1	1425	42.1
Q35: Other Vasodilators				
No	3345	98.6	3351	99.1
Yes	49	1.4	32	0.9

DIG Trial: Selected Outcomes by Treatment Group

	Placebo		Digoxin	
	N	ColPctN	N	ColPctN
Vital Status of Patient 1=Death 0=Alive				
Alive	2209	64.9	2216	65.2
Died	1194	35.1	1181	34.8
Hosp: Cardiovascular Disease				
No Event	1553	45.6	1703	50.1
First Event	1850	54.4	1694	49.9
Hosp: Worsening Heart Failure				
No Event	2223	65.3	2487	73.2
First Event	1180	34.7	910	26.8
Hosp: Supraventricular Arrhythmia				
No Event	3251	95.5	3264	96.1
First Event	152	4.5	133	3.9
Hosp: Myocardial Infarction				
No Event	3202	94.1	3202	94.3
First Event	201	5.9	195	5.7
Hosp: Unstable Angina				
No Event	3005	88.3	2998	88.3
First Event	398	11.7	399	11.7
Hosp: Stroke				
No Event	3239	95.2	3240	95.4
First Event	164	4.8	157	4.6
Hosp: Coronary Revascularization				
No Event	3332	97.9	3314	97.6
First Event	71	2.1	83	2.4

Supplement: SAS Code to reproduce results of NEJM paper.

Note that while most baseline variables were permuted among patients within a treatment group, sex and race were not permuted. Treatment effects within sex and race should be preserved.

The DIG teaching dataset is being provided in SAS version 6.12 and SAS transport (for use in statistical software packages other than SAS) formats.

The following SAS code will read in the dataset, create necessary formats, and reproduce the counts and percentages found in the NEJM paper. The 'libname' statement would need to be altered to reflect where the data is stored on your machine or file server:

```
libname dig v612 'C:\digdata\';



proc format;
 value incr  0='No Event'
             1='First Event';

 value dth2r  0='Alive'
              1='Died';

 value trtr 0='Placebo'
            1='Digoxin';

 value sexr 1='Men'
            2='Women';

 value racer 1='White'
             2='Non-white';

 value methr 1='Radionuclide'
             2='Angiography'
             3='2-D Echo';

 value chestr 1='<=0.55'
              2='>0.55';

 value functr 1='Class I'
              2='Class II'
              3='Class III'
              4='Class IV';

 value etiolr 1='Ischemic'
              2='Hypertensive'
              4='Idiopathic'
              7='Other';

 value dthr 1='Worsening Heart Failure'
            2='Other Cardiac'
            3='Other Vascular'
            4='Unknown'
            5='Noncardiac, nonvascular';

 value yesno 0='No'
             1='Yes';
```

```
 value ejfr 1='0.25-0.45'
            2='<0.25';

 value causer 1='Ischemic'
              2='NonIsch.';

 value funct2r 1='NYHA I,II'
               2='NYHA III,IV';


data dig; set dig.dig;

/* REFORMATS FOR SUMMARY TABLES */
 if 0<chestx<=0.55 then ctratio=1; if chestx>0.55 then ctratio=2;
 if nsym>=4 then nsym=4;
 if chfetiol=1 then chfcause=1; if chfetiol=2 then chfcause=2;
   if chfetiol=4 then chfcause=4; if chfetiol=3 or chfetiol=5 or chfetiol=6
then chfcause=7;
 if diuretk=1 or diuret=1 then diuretic=1; if diuretk=0 and diuret=0 then
diuretic=0;

 if 0<ejf_per<25 then ejfgrp=2; if 25<=ejf_per<=45 then ejfgrp=1;
 if functcls in(1,2) then NYHAgrp=1; if functcls in(3,4) then nyhagrp=2;
 if chfetiol=1 then cause=1; if chfetiol>1 then cause=2;



* MEANS AND PROPORTIONS FOR NEJM TABLES 1-4 ;

proc tabulate data=dig noseps formchar=' __________' missing;
 class trtmt ;
 format trtmt trtr. ;
 var age ejf_per chfdur nhosp;
 tables age ejf_per chfdur nhosp,
      trtmt*((N *f=6.0) (mean *f=6.2) (median *f=6.1) (std *f=6.2))
            /condense rtspace=32 box='Means found in DIG Trial Tables 1 and
2';
run;


proc tabulate data=dig noseps formchar=' __________' missing;
 class trtmt sex race ejfmeth ctratio functcls nsym prevmi angina diabetes
hyperten diguse chfcause diuretic aceinhib nitrates vasod digdose reason;
 format trtmt trtr. sex sexr. race racer. ejfmeth methr. ctratio chestr.
functcls functr. prevmi yesno. angina yesno. diabetes yesno. hyperten yesno.
diguse yesno. chfcause etiolr. diuretic yesno. aceinhib yesno. nitrates yesno.
vasod yesno. reason dthr.;
 tables sex race ejfmeth ctratio functcls nsym prevmi angina
   diabetes hyperten diguse chfcause diuretic aceinhib nitrates vasod digdose
reason,
      trtmt*((N *f=8.0) (colpctn *f=8.1))
            /condense rtspace=42 box='Proportions: DIG Trial Tables 1 and 2';
run;
```

```
proc tabulate data=dig noseps formchar=' __________' missing;
 class trtmt cvd whf vena sva dig mi uang strk crev rinf oth hosp;
 format cvd incr. whf incr. vena incr. sva incr. dig incr. mi incr. uang incr.
   strk incr. crev incr. rinf incr. oth incr. hosp incr. trtmt trtr.;
 tables cvd whf vena sva dig mi uang strk crev oth rinf hosp,
      trtmt*((N *f=8.0) (colpctn *f=8.1))
            /condense rtspace=42 box='Proportions: DIG Trial Table 3';
run;


proc tabulate data=dig noseps formchar=' __________' missing;
 class trtmt dwhf ejfgrp diguse cause ctratio nyhagrp;
 format trtmt trtr. dwhf incr. ejfgrp ejfr. diguse yesno.
   cause causer. ctratio chestr. nyhagrp funct2r.;
 tables ejfgrp diguse cause ctratio nyhagrp,
      trtmt*dwhf*((N *f=7.0) (pctn<dwhf> *f=7.1))
            /condense rtspace=32 box='Proportions: DIG Trial Table 4';
run;

* PRINT A TABLE OF RR FROM COX MODELS (NEJM TABLE 3);

proc datasets nolist; delete all;run; *removes dataset if it already exists.
This statement must be executed if re-running program;

*Below is Macro to calculate HRRs found in table 3. Note some HRR are
different from manuscript due to combining certain outcomes;
%macro tab3(var, vardays);

* proportional hazards model. output dataset has 2 obs: beta coefficient and
variance of beta;
proc phreg data=dig noprint outest=phout covout;
    model &vardays*&var(0)=trtmt;
    run;

proc transpose data=phout out=out prefix=beta; var trtmt; *put beta coeff and
var on same row;
data out; set out;
 outcome="&var  ";
 HRR=exp(beta1);                    *hazard rate ratio;
 waldx2=(beta1/sqrt(beta2))**2;     *wald chi square statistic;
 pvalue=1-probchi(waldx2,1);        *P-value ;
 ll=exp(beta1-(1.96*sqrt(beta2)));  *lower limit of HRR;
 ul=exp(beta1+(1.96*sqrt(beta2)));  *upper limit of HRR;

proc append base=all data=out force;run;
%mend;

%tab3(cvd, cvddays);
%tab3(whf, whfdays);
%tab3(vena, venadays);
%tab3(sva, svadays);
%tab3(dig, digdays);
%tab3(mi, midays);
%tab3(uang, uangdays);
%tab3(strk, strkdays);
%tab3(crev, crevdays);
%tab3(ocvd, ocvddays);
%tab3(rinf, rinfdays);
%tab3(oth, othdays);
%tab3(hosp, hospdays);

proc print data=all;
 Title 'HRR for NEJM Table 3';
 var outcome hrr waldx2 pvalue ll ul;run;
```

```
* PRINT A TABLE OF RR FROM COX MODELS (NEJM TABLE 4);

*Create interaction terms. Considering treatment and covariate as dichotomous
groups, interaction term is where treatment=digoxin and covariate is at high
risk level;

data dig; set dig;
 if 0<ejf_per<25 then ejfgrp=1; if 25<=ejf_per<=45 then ejfgrp=0;
 if diguse=1 then prevdig=0; if diguse=0 then prevdig=1;
 if chfetiol=1 then cause=0; if chfetiol>1 then cause=1;
 if 0<chestx<=0.55 then ctratio=0; if chestx>0.55 then ctratio=1;
 if functcls in(1,2) then NYHAgrp=0; if functcls in(3,4) then nyhagrp=1;

 ejfint=ejfgrp*trtmt; digint=prevdig*trtmt; chfint=cause*trtmt;
 ctint=ctratio*trtmt; nyhaint=nyhagrp*trtmt;


proc datasets nolist; delete all2;run;
*removes dataset if it already exists. This statement must be executed if re-
running program;


*Below is Macro to calculate HRRs found in table 4;
%macro tab4(var, int, label1, label2);

* proportional hazards model. output dataset has 4 obs: 1 row for beta
coefficients and 3 rows for var-covar matrix;
proc phreg data=dig noprint outest=phout covout;
    model dwhfdays*dwhf(0)=trtmt &var &int;
     run;

* Manipulate output dataset so that dataset rows match table 4 rows
for each variable;
data beta; set phout; if _type_='PARMS';int=&int;
data var1; set phout; if _type_='COV' and _name_='TRTMT';
 setrt=sqrt(trtmt); keep setrt _LNLIKE_;
data var2; set phout; if _type_='COV' and _name_="&int";
 seint=sqrt(&int); keep seint _LNLIKE_;
data covar; set phout; if _type_='COV' and _name_='TRTMT';
 covar=2*(&int); keep covar _LNLIKE_;
data row1; merge beta var1 ; by _LNLIKE_;row="&label1   "; keep row trtmt
setrt;
data row2; merge beta var1 var2 covar; by _LNLIKE_;
  row="&label2   ";
  trtmt=trtmt+&int; setrt=sqrt(setrt**2+seint**2+covar);
   keep row trtmt setrt int seint;

* combine rows and calculate statistics of interest for each variable;
data out; set row1 row2;
 HRR=exp(trtmt);                    *hazard rate ratio;
 waldx2=(trtmt/setrt)**2;           *wald chi square statistic;
 pvalue=1-probchi(waldx2,1);        *P-value ;
 pvint =1-probchi((int/seint)**2,1);  *P-value for interaction ;
 ll=exp(trtmt-(1.96*setrt));        *lower limit of HRR;
 ul=exp(trtmt+(1.96*setrt));        *upper limit of HRR;
run;

proc append base=all2 data=out force;run;
%mend;
```

```
%tab4(ejfgrp, ejfint, EJF25_45, EJFLT25);
%tab4(prevdig, digint, PRIORDIG, NOPRIORDIG);
%tab4(cause, chfint, ISCHEMIC, NONISCHEMC);
%tab4(ctratio, ctint, CTRATLE55,CTRATGT55 );
%tab4(nyhagrp, nyhaint, NYHA1OR2, NYHA3OR4);


proc print data=all2;
 Title 'HRR for NEJM Table 4';
 var row hrr waldx2 pvalue ll ul pvint;run;
```