

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.

DIGITALIS INVESTIGATION GROUP
BASELINE FORM

NHLBI-VA Study #995
Revised FEB 1992

Local Center Name _____

Randomization Number

PRINT Patient Name _____ ID _____

Date of Randomization Mo ____ Day ____ Yr ____
Last First M.I.

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 - not to be transmitted by telephone.

12. APPROXIMATE DURATION OF CHF (months) **CHFDUR**
SIGNS OR SYMPTOMS: 0=None or Unknown, 1=Present, 2=Past, 3=Present and Past
(Present is defined as \leq 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. S₃ **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) **FUNCCLAS**
 - 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): $\text{INT}(\text{Date of Randomization} - \text{Date of Birth}) / 365.25$

BMI (Body Mass Index): $\text{Weight in kg} / \text{Height in meters}^2$

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

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=NODays 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 STRKDAY
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 OCVDAYS
- &14. OTHER CARDIOVASCULAR REASON, SPECIFY OCVD OCVDAYS
15. RESPIRATORY INFECTION RINF RINF DAYS
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 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, Arrhythmia, 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, Bradyarrhythmia 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
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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	RINF DAYS	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: Systolic 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