

Nine Cell Laboratory Tables(c)

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INTRODUCTION: This paper and the concept it advocates are a response to a functional/management problem existing throughout the pharmaceutical industry. The ability to reliably review laboratory data arriving from clinical investigational sites. It is suggested that this concept will help both pharmaceutical companies and contract research organizations minimize the potential adverse effects of human factors in reviewing laboratory data.

BACKGROUND: In 1993 multicentered clinical studies were underway with a new clinical entity fialuridine (FIAU). The studies were going along and results were arriving at the sponsor's offices. Unfortunately, somewhere along the way five patients contracted severe liver and pancreatic injury and died. The patients died in different centers and the causes of death were such that no red flag was immediately raised relative to the deaths. Another element complicating the situation was that laboratory data typically arrives as studies are being concluded. No one was rapidly able to connect the fact that these patients may have been possibly dying from the study drug, in time to suspend clinical studies.

Clinical studies usually are large. It is not uncommon to have scores or hundreds of patients. Clinical Research Assistants travel to study sites to review case report forms, gather the case report forms and retrieve them with data recorded. This invariably is happening under a cloud of incredible pressure from management.

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-- be it from a pharmaceutical company or from a contract research organization. The 'gathering' of data from clinical study sites is stressful by itself, but the 'time-pressure' added by management aggravates the collection process.

It is important to know that laboratory data requires that Clinical Research Assistants or Data Analysts review the laboratory data usually manually, or effectively manually. That is they look at laboratory results for each patient. This requires that each person involved must look at the results and compare the laboratory results with 'normals' for each test in the lab screen. This becomes tedious quickly. There can be as few as 10-12 to as many as 40 or 50 tests and to review all these 'normals' requires that a reviewer keep these figures close at hand or memorize the set. Laboratory samples and runs are made at varying frequency throughout a clinical study. In short studies, there may be only two sets of lab samples run. In longer studies there may be a half dozen, dozen or more lab specimens run. Yes, there are many, many printouts done by data managers to produce listings that attempt to serve the requirements to assist those reviewing this laboratory data. This normally happens as a study progresses but is not a totally reliable way to 'monitor' a study.

Not only does laboratory data have to be reviewed, but ALL the data that is being collected during the conduct of a study must be assembled and reviewed. This data must be reviewed, maybe returned to the investigational site and possibly re-entered in a database, verified and checked. There is performance pressure, travel to multiple study sites and there is usually considerable interest from management to 'get this in and done'!

The final piece of the matrix: The Food and Drug Administration (FDA). The FDA requires that all laboratory data presentations for every patient must be accomplished in two forms: By Patient and By Test. That is, every test done for every patient is to be listed twice.w

METHODS: It is the author's opinion that this is the place for a semi-graphical approach to data review. Attendees here will, no doubt, agree that a picture is worth at least a thousand words. That is the premise behind the nine-cells. Sets of laboratory data taken in pairs to create the plots. (Figure 1: Nine cells. Axis swap).

The focal point of these nine cells is the By Test Listing. Data in only one cell of the nine requires no action; that occurring in the other eight cells are out-of-bounds. These eight are those that are of real interest. The sequel question is: Why? ...that is what clinical people must research to answer.

Here is an example, from a small study. Laboratory data is frequently divided into three sections: Chemistry, Hematology and Urinalysis, as it was here. Chemistry here includes: Calcium (CALCIUM), sodium (SODIUM), potassium (K), chloride (CHLO), aspartate aminotransferase [sometimes now AST] (SGOT), bilirubin (BILI), alanine aminotransferase [sometimes now ALT] (SGPT), alkaline phosphatase (ALK_PHOS), [blood] urea nitrogen (BUN), creatinine (CREAT), glucose (GLUCOSE), lactate dehydrogenase [sometimes LD] (LDH). Hematology here includes: Hemoglobin (HGB), hematocrit (HCT), platelets (PLATELET), white blood cells (WBC), neutrophils (NEUT), lymphocytes (LYMPHS), monocytes (MONOS), eosinophils (EOS), basophils (BASOS). Urinalysis here was very small, with only two measures:

Specific gravity (SPECGRAV) and urinary pH (PH). A total of 23 tests. A small study, particularly when these tests were run only twice during the study. Testing was done prior to study drug administration and at the conclusion of the study. This is adequate to demonstrate the approach.

The proposition here is one of printing a graphical presentation that allows SAS to paint the 'out-of-bounds' values, but also supplements this with a listing of ONLY those observations that are out-of-bounds. If none are out of limits, no listing. This is then done for each of the laboratory tests that are run in the clinical series. That is if there are 23 tests run twice for each patient, then there will be only 23 tables. There is a minimum of one page per test, there will be two pages per test IF a value is out of range. Remember, this speaks only to the By Test Listing; there will also be a page (or more) for each By Patient Listing. This report now is to a minimum of 36 pages - 13 patients plus 23 tests.

There are several tables that you will see. Notice that each is indexed through a numbering sequence. It is most important that every page be addressable in a report, and later in an New Drug Application (NDA's). Notice also the titles. There is quite a bit of information given to the reader. This is very important in summarizing data of this nature for submission to FDA. NDA's are submitted to the FDA in triplicate. Every effort to precisely and uniquely identify a page helps FDA review new drug applications. If the FDA can be helped, the FDA can review an application faster. The fewer questions the reviewer has, the faster the review can proceed. A faster review can literally mean millions of dollars to sponsoring companies. They can get the new drug to the market faster, this is where the dollars accumulate: Being there first.

Examining some specimen pages: These contain a lot of identifying information:

First, The By Patient Listing: This is relatively straight forward. The best solution is to print every data item for every patient on a single page per patient, if possible. This requires ingenuity, literally 'shoe spooning' every possible data point for a patient onto one page. Physicians love this output - they are accustomed to reviewing one patient at a time. There were 12 patients analyzed in this (small) study, then there will be at least 12 pages in this part of the report. As clinical reports go, an extremely small study. This By Patient listing is mainly for physicians. (Figure 2: By Patient Listing).

The By Patient Listing contains Patient identification number, age, race and treatment sequence. The sequence in crossover studies sometimes substitutes for treatment group in parallel group studies. Age and Race are included here, but all participants in this study were males. Sex will be added with a mixed sex study. All of this because laboratory standards vary by age, sex and race. Differing lab standards are providing for this, again more to help the reviewer. Anecdotal medical reports speak of 'A x-year old, race, sex presented with ...'. It seems only reasonable to provide the same information here on the patient summary.

Next, The By Test Listing: This is fraught with possibilities. There are many who believe that this is the place for statisticians to 'take over' and apply a multitude of statistical tests to data whether they make sense or not. Many plain listings are tried, and with computer screening and listing there is still the difficulty that detailed reading is required. Despite lots of flags attached to out-of-bounds values. (Figures 3 & 4: By Test).

The By Test Listing contains identifying information of a slightly different type. The By Patient Listing addresses the patient. This By Test Listing addresses the test. Identified here are the test, the units as any good scientist will provide the units and the 'N.R.' up to the right provides the 'Normal Range' that is being used. The SAS legend A = 1 obs, B = 2 obs,... etc. Then the plot. Notice as we go through these tables:

- (1) The identification provided as discussed earlier to help writers write for reviewers to read and interpret the tables be it the plot or the summary,
- (2) The shifting bounds of the plot. The plot centers around the central cell (N-N). The magnitude of the other eight cells depends on whether they are occupied or not,
- (3) The 'border values' these are dependent on whether or not 'greater than or equal to' (GE) or 'greater than' (GT) were used, if GE there will be values on the boundary. The same discussion applies to the 'less than or equal to' (LE) or 'less than' (LT) operators. This is a medical decision. If a physician wants 'greater than or equal to' then there will be border values.

We will now look through several tables. Notice how your comfort level increases after you have looked at the first two or three. This is a very intuitive approach. Plus it is factual and helpful in determining trends. If one patient is listed frequently, that patient must be watch closely for the balance of the study. Lets start, please raise your questions as they occur. There will be a quiz at the end. Pay close attention. (Figures 5A - 10B).

CONCLUSION: It is believed that this is a rapidly intuitive system of reviewing laboratory data. Those assigned to review case report forms and laboratory data will find that this is a rapidly assimilated battery of tables. That it grows easier with short term application.

FUTURE DIRECTION: The next revision, already done and working, will look inside the center cell, 'N-N', and find values that are increasing or decreasing chosen amounts, say 10/15%. We have all seen patients whose values start normal and climb, or start normal and decrease; but stay within the normal range. No action has generally been taken on these cases because 'Both values were normal'. We all know this is not an entirely appropriate situation. It is suggested this is the way to address those 'Wandering Normals'.

NINE CELL LABORATORY TABLES (A)

S C R E E N I N G	H - L	H - N	H - H
	N - L	N - N	N - H
	L - L	L - N	L - H

E X I T

NINE CELL LABORATORY TABLES (B)

E X I T	L - H	N - H	H - H
	L - N	N - N	H - N
	L - L	N - L	H - L

S C R E E N I N G

(dead space to blank SAS information)
 SPONSOR'S CORPORATE NAME, INC. (generic drug name)
 Protocol title line no. 1
 Protocol title line no. 2

APPENDIX E-1: INDIVIDUAL SUBJECT DETAILS

AGE = 23 TMTSEQ = ██████████ RACE = Caucasian

SUBJ=1*

TEST	PRESTUDY	POSTSTDY
HGB	16.000	15.900
HCT	49.000	48.200
PLATELET	190.000	184.000
WBC	3.900	3.800
NEUT	52.000	62.000
LYMPHS	38.000	30.000
MONOS	7.000	6.000
EOS	2.000	2.000
BASOS	1.000	.
CALCIUM	9.600	9.500
K	4.800	3.900
SODIUM	144.000	143.000
CHLO	105.000	104.000
SGOT	28.000	24.000
BILI	0.600	0.700
SGPT	18.000	14.000
ALK_PHOS	80.000	83.000
BUN	13.000	14.000
CREAT	1.100	1.200
GLUCOSE	87.000	76.000
LDH	117.000	122.000
SPECGRV	1.025	1.025
PH	5.000	6.000

FIGURE 2

Information/explanatory footnote1
 Information/explanatory footnote2
 Information/explanatory footnote3

(dead space to blank SAS information)
 SPONSOR'S CORPORATE NAME, INC. (generic drug name)
 Protocol title line no. 1
 Protocol title line no. 2

FIGURE E-2B: CHEMISTRY [SODIUM (meq/dl) N.R. 136-145]
 Plot of PRESTUDY*POSTSTDY. Legend: A = 1 obs, B = 2 obs, etc.

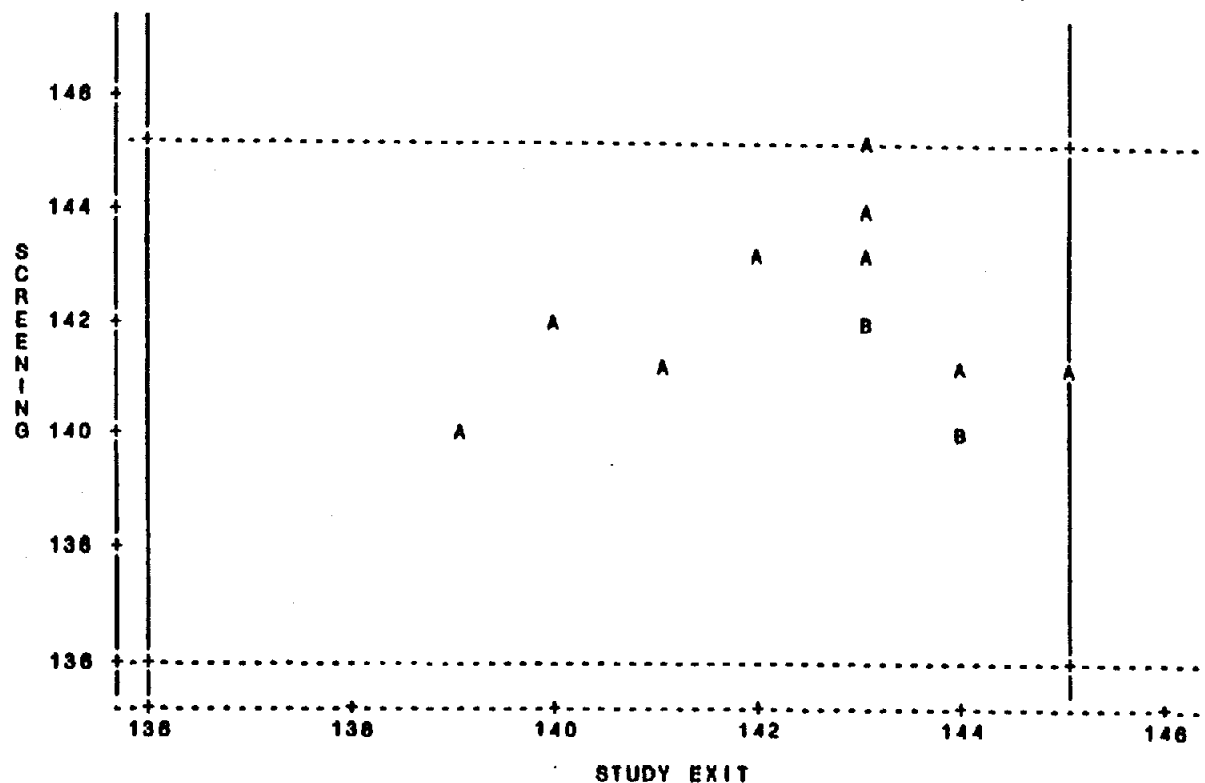


FIGURE 3

Information/explanatory footnote1
 Information/explanatory footnote2
 Information/explanatory footnote3

(dead space to blank SAS information)
SPONSOR'S CORPORATE NAME, INC. (generic drug name)
Protocol title line no. 1
Protocol title line no. 2

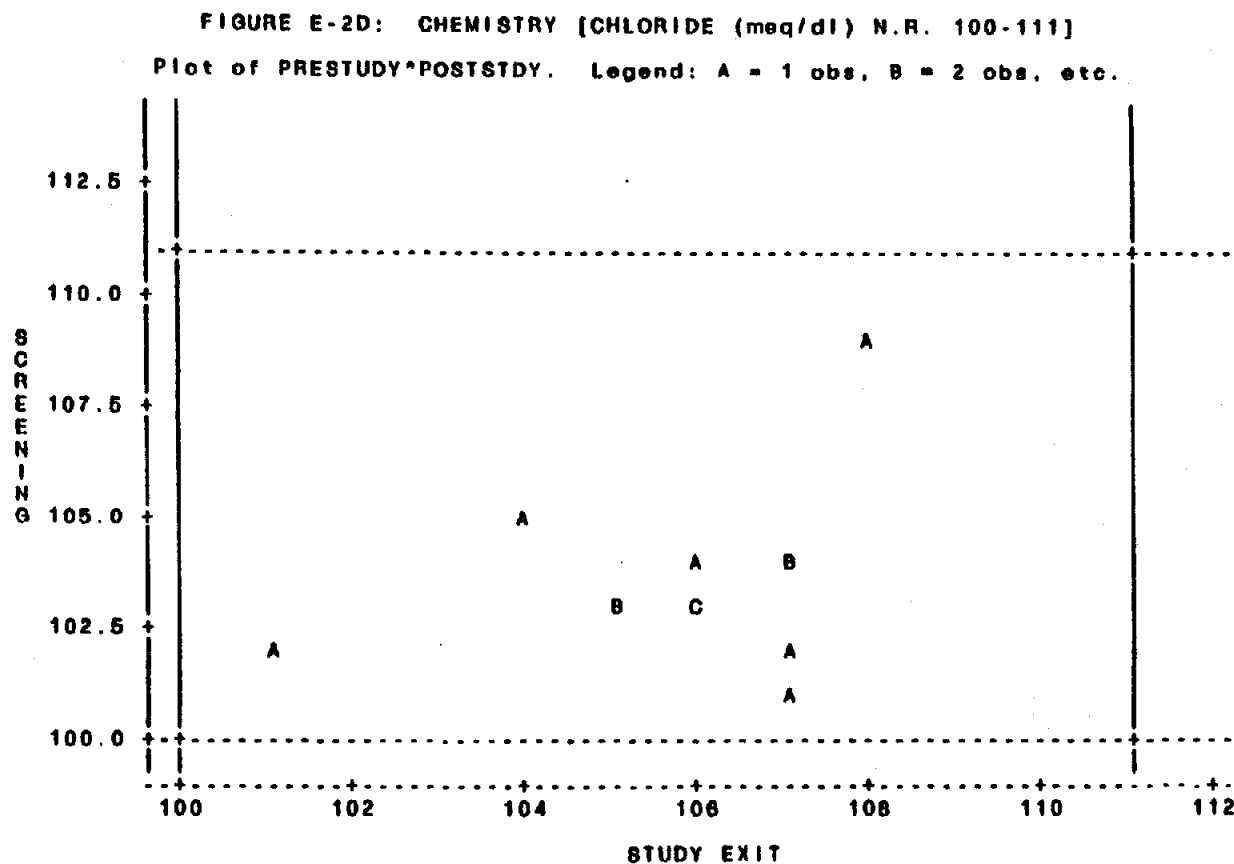


FIGURE 4

Information/explanatory footnote1
Information/explanatory footnote2
Information/explanatory footnote3

(dead space to blank SAS information)
SPONSOR'S CORPORATE NAME, INC. (generic drug name)
Protocol title line no. 1
Protocol title line no. 2

FIGURE E-2F: CHEMISTRY (TOTAL BILIRUBIN (mg/dl) N.R. 0.0-1.5)
Plot of PRESTUDY*POSTSTDY. Legend: A = 1 obs, B = 2 obs, etc.

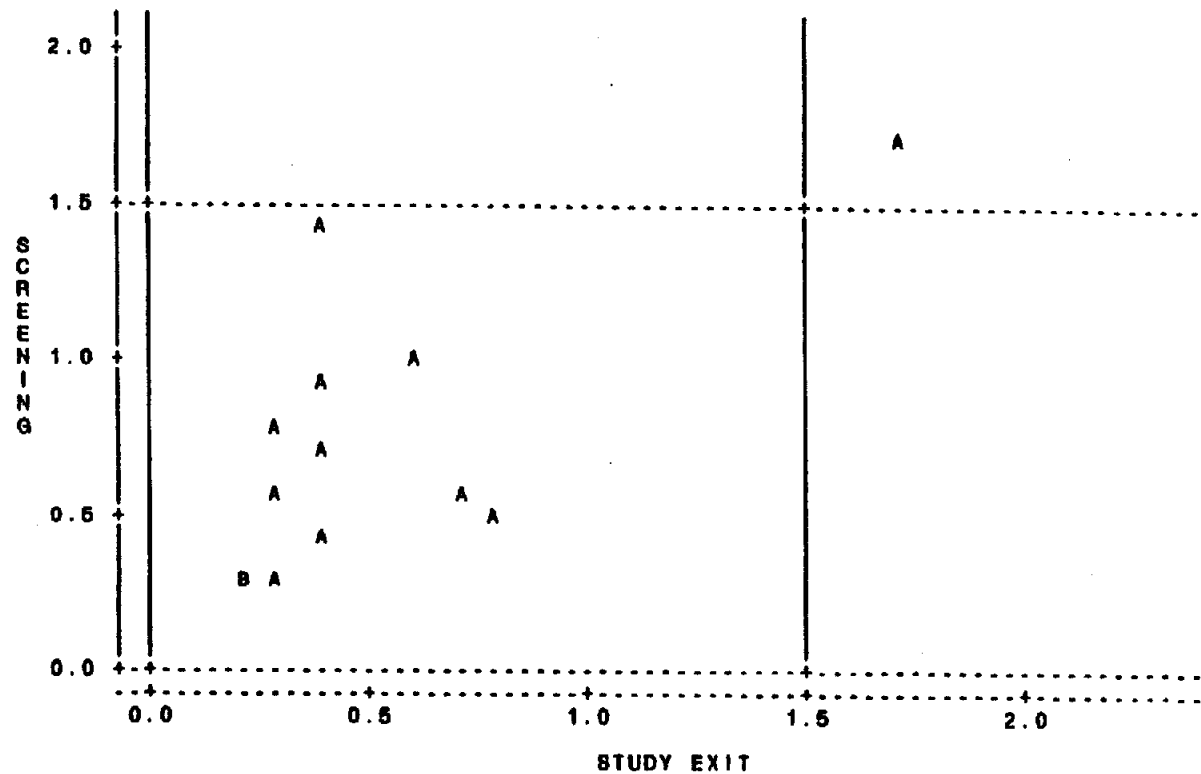


FIGURE 5 A

Information/explanatory footnote1
Information/explanatory footnote2
Information/explanatory footnote3

(dead space to blank SAS information)
SPONSOR'S CORPORATE NAME, INC. (generic drug name)
Protocol title line no. 1
Protocol title line no. 2

FIGURE E-2F: CHEMISTRY [TOTAL BILIRUBIN (mg/dl) N.R. 0.0-1.5]

ABNORMAL LABORATORY VALUES

SUBJ	SCREENING	STUDY EXIT
9	1.7	1.7

FIGURE 5 B

Information/explanatory footnote1
Information/explanatory footnote2
Information/explanatory footnote3

(dead space to blank SAS information)
SPONSOR'S CORPORATE NAME, INC. (generic drug name)
Protocol title line no. 1
Protocol title line no. 2

FIGURE E-2K: CHEMISTRY [GLUCOSE (mg/dl) N.R. 70-110]
Plot of PRESTUDY*POSTSTDY. Legend: A = 1 obs, B = 2 obs, etc.

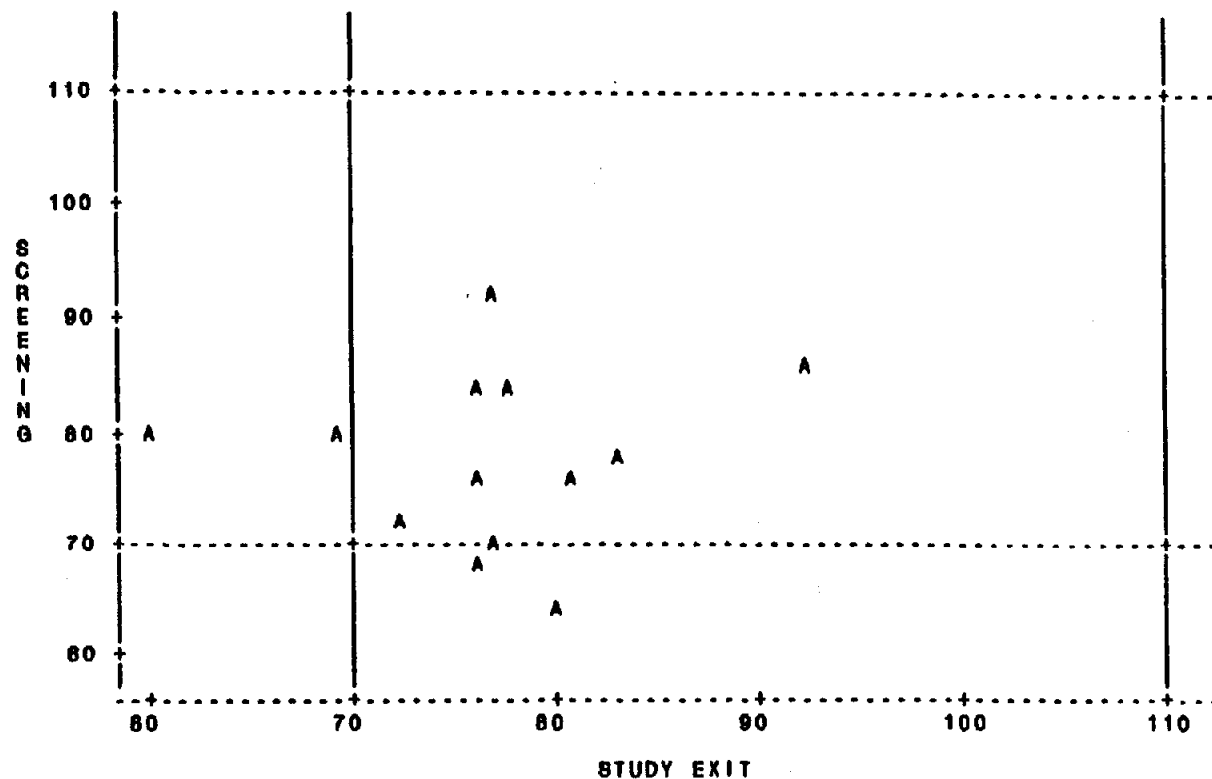


FIGURE 6 A

Information/explanatory footnote1
Information/explanatory footnote2
Information/explanatory footnote3

(dead space to blank SAS information)
SPONSOR'S CORPORATE NAME, INC. (generic drug name)
Protocol title line no. 1
Protocol title line no. 2

FIGURE E-2K: CHEMISTRY [GLUCOSE (mg/dl) N.R. 70-110]

ABNORMAL LABORATORY VALUES

SUBJ	SCREENING	STUDY EXIT
1*	87	76
4	79	89
8	79	80
11	84	80

FIGURE 6 B

Information/explanatory footnote1
Information/explanatory footnote2
Information/explanatory footnote3

(dead space to blank SAS information)
SPONSOR'S CORPORATE NAME, INC. (generic drug name)
Protocol title line no. 1
Protocol title line no. 2

FIGURE E-3A: HEMATOLOGY [HEMAGLOBIN (g/dl) N.R. 13.5-18.0]
Plot of PRESTUDY*POSTSTDY. Legend: A = 1 obs, B = 2 obs, etc.

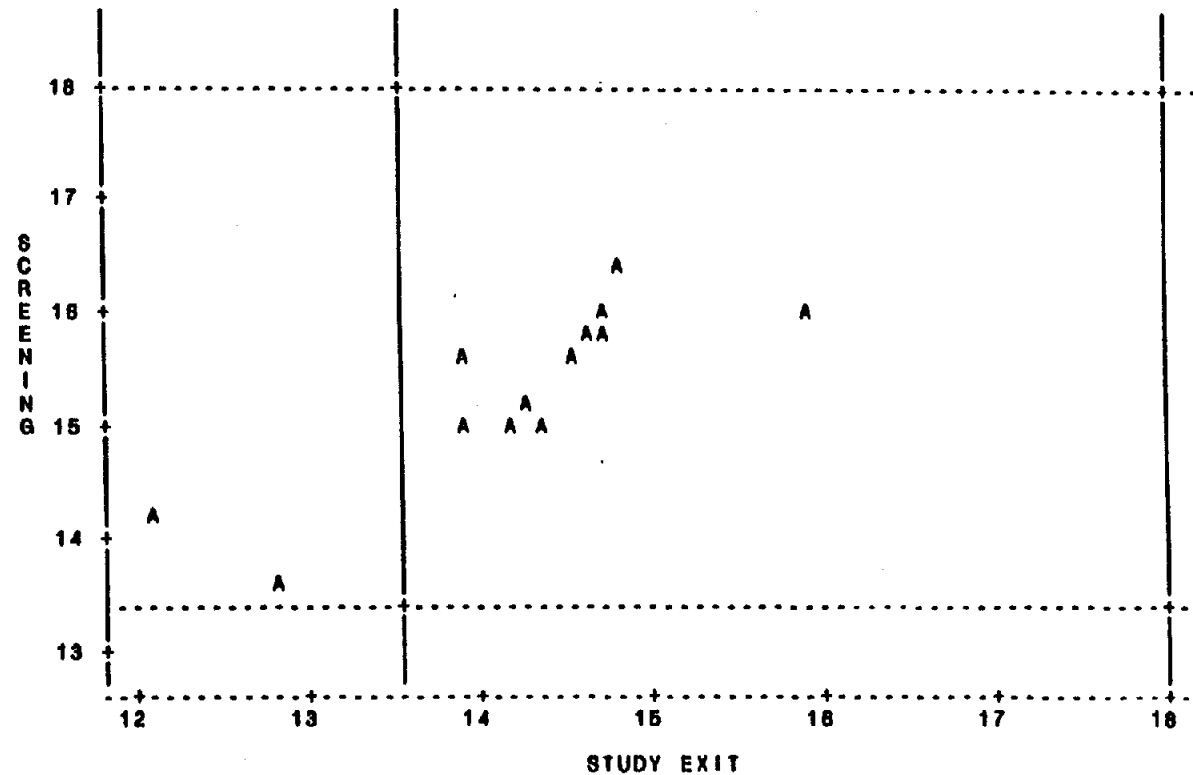


FIGURE 7 A

Information/explanatory footnote1
Information/explanatory footnote2
Information/explanatory footnote3

(dead space to blank SAS information)
SPONSOR'S CORPORATE NAME, INC. (generic drug name)
Protocol title line no. 1
Protocol title line no. 2

FIGURE E-3A: HEMATOLOGY [HEMAGLOBIN (g/dl) N.R. 13.5-18.0]

ABNORMAL LABORATORY VALUES

SUBJ	SCREENING	STUDY EXIT
8	14.3	12.1
901	13.6	12.8

110

FIGURE 7 B

Information/explanatory footnote1
Information/explanatory footnote2
Information/explanatory footnote3

(dead space to blank SAS information)
 SPONSOR'S CORPORATE NAME, INC. (generic drug name)
 Protocol title line no. 1
 Protocol title line no. 2

FIGURE E-3D: HEMATOLOGY [WBC ($10^3/\text{mm}^3$) N.R. 4.8-11.0]
 Plot of PRESTUDY*POSTSTDY. Legend: A = 1 obs, B = 2 obs, etc.

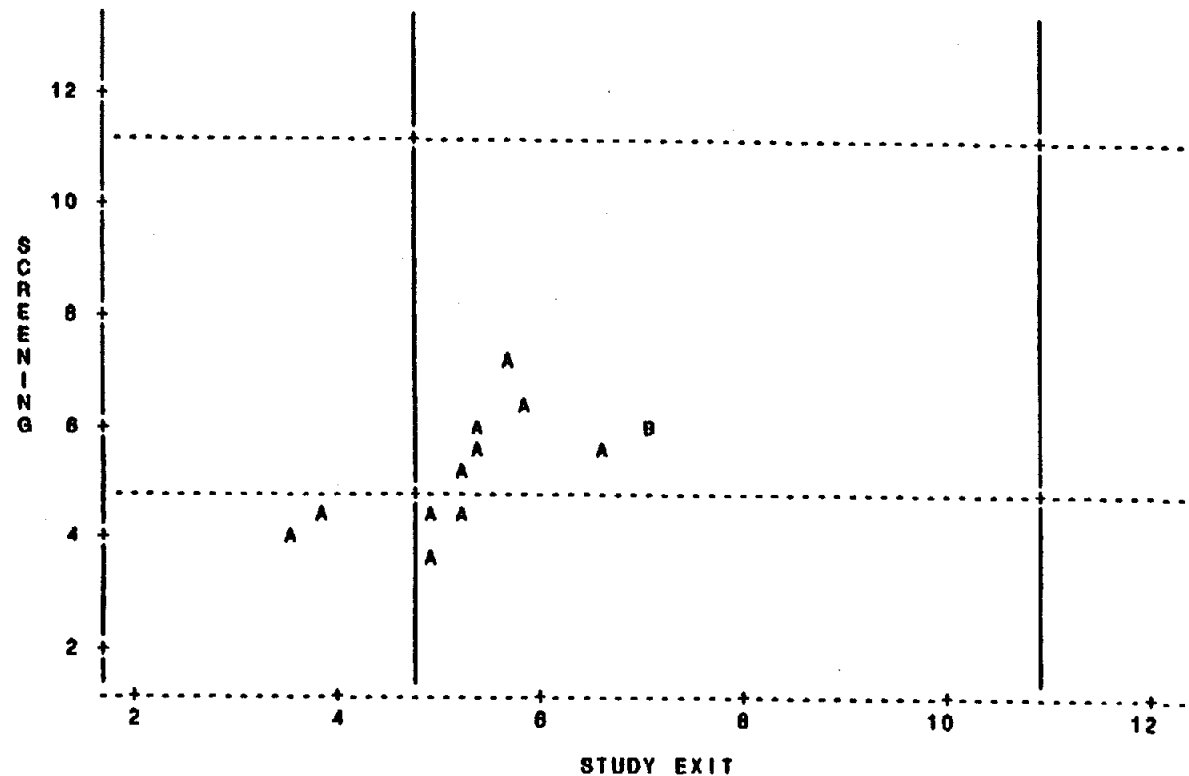


FIGURE 8 A

Information/explanatory footnote1
 Information/explanatory footnote2
 Information/explanatory footnote3

(dead space to blank SAS information)
SPONSOR'S CORPORATE NAME, INC. (generic drug name)
Protocol title line no. 1
Protocol title line no. 2

FIGURE E-3D: HEMATOLOGY [WBC ($10^3/\text{mm}^3$) N.R. 4.8-11.0]

ABNORMAL LABORATORY VALUES

SUBJ	SCREENING	STUDY EXIT
1*	3.9	3.6
6	3.8	4.9
7	4.5	4.9
9	4.3	3.8
901	4.3	5.3

112

FIGURE 8 B

Information/explanatory footnote1
Information/explanatory footnote2
Information/explanatory footnote3

(dead space to blank SAS information)
 SPONSOR'S CORPORATE NAME, INC. (generic drug name)
 Protocol title line no. 1
 Protocol title line no. 2

FIGURE E-3E: HEMATOLOGY [POLYMORPHS (%) N.R. 42-72]
 Plot of PRESTUDY*POSTSTDY. Legend: A = 1 obs, B = 2 obs, etc.

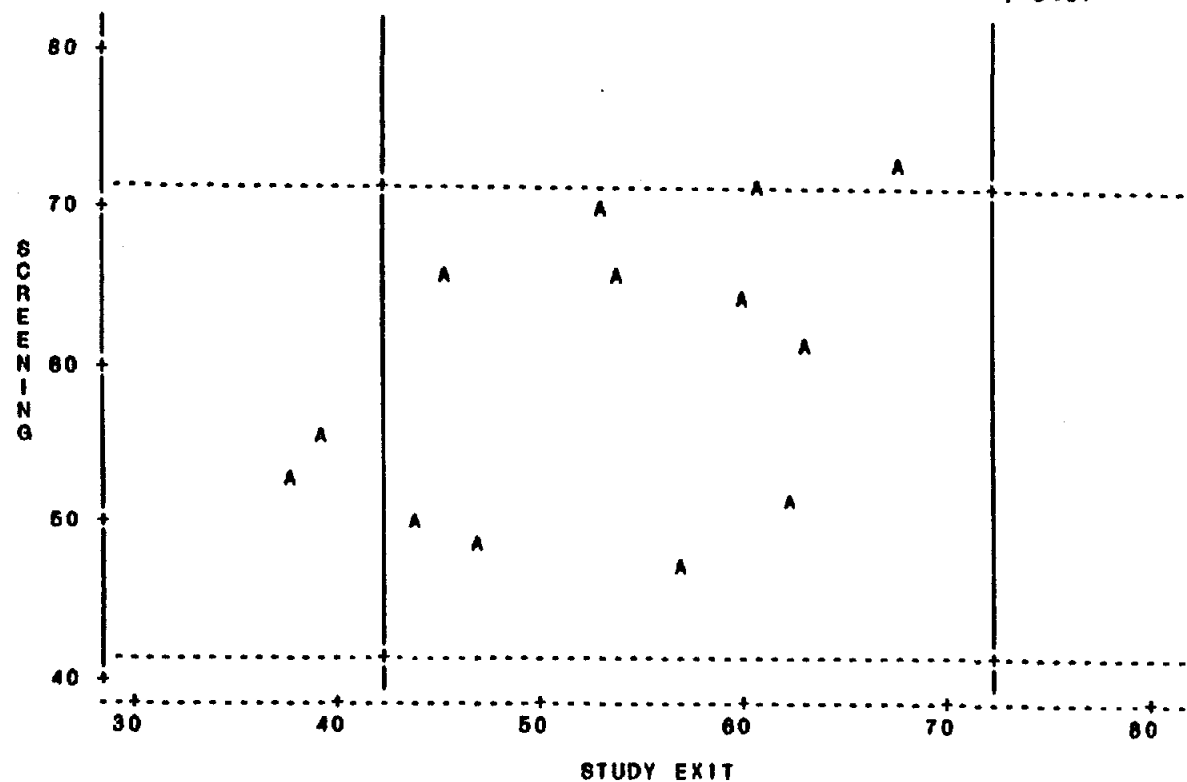


FIGURE 9 A

Information/explanatory footnote1
 Information/explanatory footnote2
 Information/explanatory footnote3

(dead space to blank SAS information)
SPONSOR'S CORPORATE NAME, INC. (generic drug name)
Protocol title line no. 1
Protocol title line no. 2

FIGURE E-3E: HEMATOLOGY [POLYMORPHS (%) N.R. 42-72]

ABNORMAL LABORATORY VALUES

SUBJ	SCREENING	STUDY EXIT
2	53	38
9	56	39
10	73	88

114

FIGURE 9 B

Information/explanatory footnote1
Information/explanatory footnote2
Information/explanatory footnote3

(dead space to blank SAS information)
SPONSOR'S CORPORATE NAME, INC. (generic drug name)
Protocol title line no. 1
Protocol title line no. 2

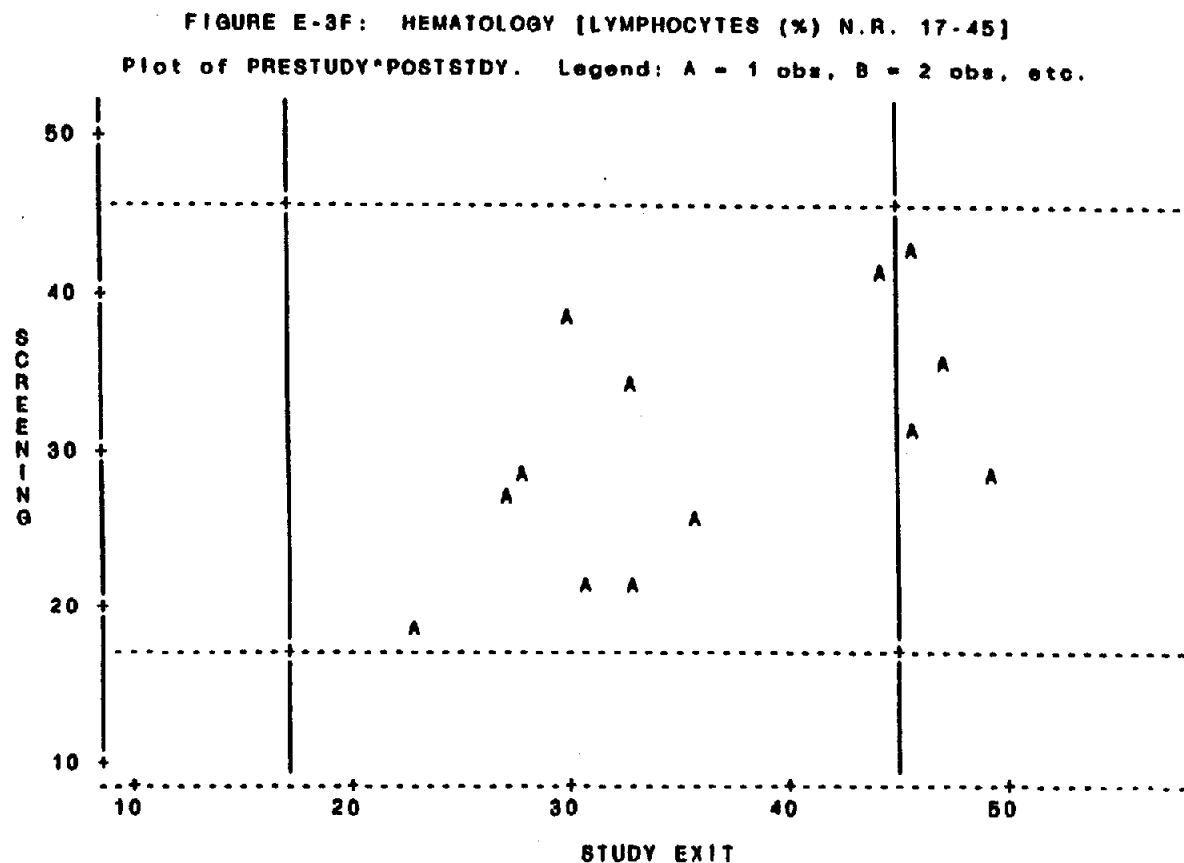


FIGURE 10 A

Information/explanatory footnote1
Information/explanatory footnote2
Information/explanatory footnote3

(dead space to blank SAS information)
SPONSOR'S CORPORATE NAME, INC. (generic drug name)
Protocol title line no. 1
Protocol title line no. 2

FIGURE E-3F: HEMATOLOGY [LYMPHOCYTES (%) N.R. 17-45]

ABNORMAL LABORATORY VALUES

SUBJ	SCREENING	STUDY EXIT
2	31	46
5	29	49
7	43	46
8	35	47

FIGURE 10 B

Information/explanatory footnote1
Information/explanatory footnote2
Information/explanatory footnote3