

## Paper 167-26

**Data Visualization of Phase 1 Clinical Studies—“Big AI’s World”  
or  
Using SAS<sup>®</sup> Version 8 to Acquire Quality Ice Cream**

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**ABSTRACT**

Data visualization via graphs, colorful tables and the Web can accelerate and simplify the review of data from Phase 1 clinical studies. The Output Delivery System (ODS) capability contained within Version 8 of the SAS<sup>®</sup> system provides the means by which data visualization can be achieved quickly and cost effectively.

Pfizer Global Research and Development Ann Arbor Laboratories' Phase 1 data visualization utility (“Big AI’s World”) is an application that runs on Windows NT workstations and uses a Unix host. This application makes extensive use of base SAS, SAS Graph, the Report procedure, SAS macro language and the new ODS capability. Output from this system’s execution is stored in html files on a shared server that is accessed via the Pfizer Intranet by interested clients (physicians, clinical scientists, study coordinators, and medical writers).

**INTRODUCTION**

An old adage states that a single picture is worth a 1000 words. The same conclusion can be said of the use of graphics, colorful tables and the Web in the assessment of data from clinical studies.

The use of ODS, graphics and charts in clinical studies serves a three-fold purpose:

1. Provide those individuals involved with a study’s conduct with more immediate or direct access to their data
2. Accelerate the data review process
3. Assist clinical scientists, study coordinators, writers, and physicians in more easily identifying what is clinically important.

At Pfizer Global Research and Development (PGRD) Ann Arbor Laboratories some Phase 1 studies can generate more than 900 pages of tabled or printed output. These are traditionally formatted, black and white paper-based listing or summary tables. Then, the challenge for the reviewer is to identify what is important (and not miss anything). In Phase 1 studies the focus is subject safety. Safety data can most often be found in assessments of adverse events, clinical laboratory parameters, and vital signs.

To streamline this review process the Clinical Reporting Systems (CRS) department of PGRD has begun to produce a battery of SAS generated Web-based graphics and reports with each completed clinical study.

**THE CHALLENGE**

In late January 2000, Dr. Allen (a.k.a. “Big AI”) Sedman (Clinical Science Head—Early Clinical Development) challenged the author to provide a “tool” by which he and his direct reports (physicians, clinical scientists and study coordinators) could review the results from clinical studies at their desk tops. As an added condition, the system should not require the end user to spend days in training, carry a multi-pound user manual, or learn a myriad of new technology.

Additionally, author-specific challenges included no available budget for added headcount and the delivery of day-to-day work had to continue in normal time frames.

To make delivery of this system both interesting and timely, a high-stakes wager was placed—data visualization at the desktop<sup>®</sup> by July 11, 2000. At risk, one gallon of Guernsey Dairy Farms chocolate almond ice cream.

**METHODOLOGY**

Should a physician or clinical scientist need to know how to merge the demographic or dosing data with the adverse event or clinical laboratory data? Or know that data coordinators and programmers call sitting blood pressure a combination of a couple of non-recognizable words: sbpsit and dbpsit?

There are several software packages in the marketplace that could meet some of the conditions of this wager. Some off-the-shelf packages are very technological and platform specific and work well with clinical data and Oracle (Clinical) databases. However, the difficulty with many of these tools is that they require the user to possess a system administrator or programmer’s knowledge of the databases created with each clinical study. Therefore, to avoid having to train our medical community the ins and outs of data programming, the Output Delivery System (ODS) capability of SAS<sup>®</sup> version 8.0 was used to deliver the required “wager” elements.

Today, with each completed study, several SAS-based programs are executed and their output is made available via a single web page lightheartedly labeled “Big AI’s World”. Below “Big AI’s” smiling picture is a list of study numbers and their associated protocol titles (e.g., 9999-99-- “A Single Dose Study of Some New and Novel Medicine in Healthy Volunteers”).

After the user clicks on a study number, a standard web page is presented (see page 5) that invites the user to click on the information category that he or she wants to review. A brief description of the available modules follows. Further, page 6 of this report provides detail of this system’s structure pictorially.

“Big AI’s World” is actually a series of macro programs that are executed by submitting the Clin Pharm Data Vision program (CPDV.sas). The programmer need only specify the study number at the time of submitting CPDV to generate these html and gif files. Data extract engines (another series of macros) and SQL are used to capture the required data from Oracle Clinical. Data extracts with each study include subject demographics (with height and weight), medication dosing, clinical laboratory results, ECG results, physical exam results, vital signs and adverse events.

The same techniques and flexibility pioneered in the data extract programming for CPWorld (see SUGI 25 paper: “Standard Reporting System for Phase 1 Clinical Trials”—Dong, Dunn, Rosson, Synowiec) are employed here.

**DEMOGRAPHICS**

The very first thing that a reviewer might want to know is what does the study population look like? Are they male or female, young or old, and are they caffeine, tobacco or alcohol users? To help the user make these assessments quickly, both a tabular report and a series of graphs are provided. The tabular report (via proc report) includes all of the detail that is collected when a subject is first enrolled in a study (subject number, assigned

treatment group, age, sex, race, height, weight, hormone status, etc.). Immediately following this table are a series of graphs (via proc gchart and hbars) that further illustrate this information. For instance one chart details the subjects in typical age groups (<18, 18-40, etc.), another details the subjects by a concatenated sex and race variable and still another details subject status at study termination (e.g., completed, withdrew due to adverse events, lack of compliance, etc.). The generation of these charts is dynamic in that if a particular variable was not collected (e.g., caffeine use) the code that produces the chart is not executed.

Fig. 1

```
%if &caffeine ne 0 %then %do;
  pattern1 c=orange;
  proc gchart data=demo;
  hbar caffeine/frame descending freq cfreq percent
  autoref clipref;
  title Distribution of Caffeine Use in &study;
  label caffeine='Caffeine Use';
  run;
  quit;
%end;
```

**ADVERSE EVENT ASSESSMENT**

The Adverse Event Assessment module provides the user with four (4) components. First, via SAS's Report procedure, a very simple table is displayed that details the number of treatment emergent adverse events that occurred during the study. These events are categorized and summarized by body system (e.g., Body as a Whole, Nervous System, Skin and Appendages, Special Senses, etc.). The reviewer can then very quickly determine via count totals (Treatment Emergent (TESS), Associated, Serious, Mild, Moderate, Severe) the most common type of negative effect possibly caused by the new medicine.

Fig. 2

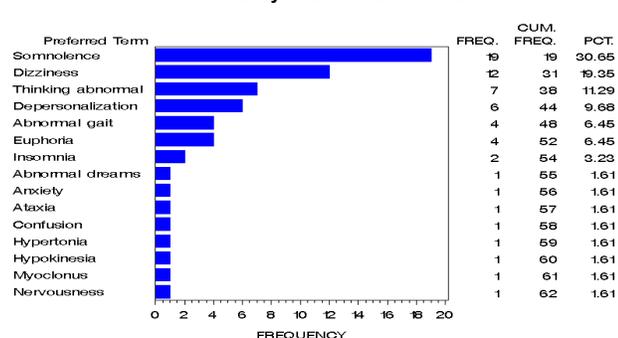
Summary of TESS ADVERSE EVENTS

Body System	TESS Adverse Events	Associated Adverse Events	Serious Adverse Events	Mild Intensity	Moderate Intensity	Severe Intensity
Body as a whole	12	7	0	8	4	0
Digestive system	4	1	0	3	1	0
Nervous system	62	58	0	45	17	0
Skin and appendages	2	0	0	1	1	0
Special senses	4	4	0	4	0	0
Urogenital system	3	1	0	2	1	0

Further, this report serves as a menu and via SAS-generated HTML links the user can then hone in or drill down on the data underlying that particular body system. After clicking on the body system name, the user sees a SAS chart (hbar) that details the preferred terms that comprise that body system. The process of assigning preferred terms involves taking investigator terms and associating them, via a dictionary, to a more common or uniform understanding of the ailment. For instance, 'pain in head', 'head pain', 'head ache' and 'headache' would all be categorized as 'headache'.

Fig. 3

Nervous System Preferred Terms

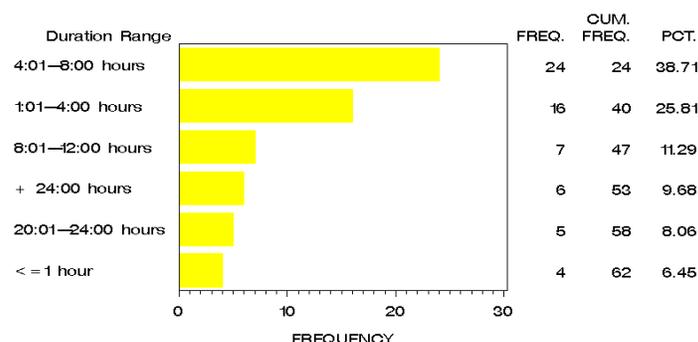


This graph is sorted in descending order, much like a pareto chart. Frequency and percent options are used with the graph so the reviewer can quickly see what each preferred term is contributing to that body system's total.

Scrolling down this page, the user will find two more charts. First, a duration chart is provided. This hbar chart details the length of time (categorically) that the adverse event lasted. Adverse Events can be an hour or less, 1:01-<4 hours, 4:01-8 hours, 8:01-12 hours, etc. These are also stacked in order of decreasing frequency so the reviewer can quickly determine that the majority of adverse events lasted a particular amount of time.

Fig. 4

Duration of TESS Adverse Events Nervous System



The next descending frequency hbar chart details the time to adverse event onset. This is measuring the amount of time from medication dosing to adverse event start. This, like the adverse event duration chart is grouped into categorical time slices.

These charts are provided at both the study and treatment group levels by merely adding a 'by group' to the chart statements. Therefore, in those studies where more than one regimen is used (a different dosing level or a different medicine) the user can easily see the events caused by that particular level or type of medicine.

The last component of the adverse event assessment module is a subject-level detailed "proc report". Through this report the user can see:

- The specific dose associated with the event
- The event's intensity, duration and time to onset
- Whether the event was felt to be associated to the study medication
- What the investigator called the event before it was decoded to a preferred term by our dictionary
- If, by definition, the event was considered to be serious

The technique used to tie this menu (Fig. 2) of overall adverse event counts to body system specific reports (Fig. 3) involves associating each body system to an html file via a proc format statement (Fig. 5). Once the 'menu' program is executed, the "proc report" generated output will display an underline under each body system name. Then, the programmer merely needs to create another report or graph or both that carries the html file name that was specified in the format statement. Once that program is executed, any time the body system name is clicked on the 'menu' takes the user directly to this linked report.

Fig. 5

```
proc format;
  value $aesys
  'Body as a whole' = '<A href=BODY.html>Body as a whole</A>'
  'Digestive system' = '<A href=DIG.html>Digestive system</A>'
  (more body systems)
  ;
run;
```

Then, this format (aesys) is used with the body system variable in the proc report statement.

```
proc report data=final split="*"
  ls=200 ps=40 nowd
  style(REPORT)={frame=box}
  style(HEADER)={background=green font_size=3}
  style(COLUMN)={foreground=#000000
  background=#9aad7 font_size=3};
col aesys tesscnt aerecnt sercnt mildcnt modcnt sevcnt;
define bodsys/ order center width=25 'Body System';
define tesscnt /center width=25 'TESS*Adverse Events';
define aerecnt /center width=25 'Associated*Adverse vents';
define sercnt /center width=25 'Serious*Adverse Events';
define mildcnt /center width=25 'Mild*Intensity';
define modcnt /center width=25 'Moderate*Intensity';
define sevcnt /center width=25 'Severe*Intensity';
format bodsys $aesys.;
title "&study.--TESS Adverse Events by Body System";
run;
```

## CLINICAL LABORATORY ASSESSMENTS

### High, Low and Average

Via the report procedure, a useful chart is provided for all numeric laboratory parameters. For each parameter the user sees by enrolled subject, the normal range, the subjects' screening measure (the pre-dose measure closest to Day 1), and the highest and lowest measure recorded during the course of the study. The study days that these highs and lows occurred on are also detailed on this simple report. Finally, the average measures during the study are detailed allowing the user to determine whether study averages exceeded or under ran the screening measures. To facilitate this understanding a percentage change column is also provided. Lastly, these data are organized in alphabetical order by lab parameter so that the user can rapidly search through them from their workstation.

### Pre-Selected Lab Graphs

The next lab component provides, via SAS graph, subject level clinical laboratory graphs (gplots) of the physician or clinical scientist's choosing. Therefore, the medical or scientific expectations need to be determined before executing this module of the program. For instance, if a diabetic drug is being studied, then fasting serum glucose might be graphed with every study involving this new medication. In dealing with healthy subjects one might not see a parameter fall out of range. However, we may see a difference within range and viewing this information pictorially makes this identification much easier.

In addition to the subject's upper and lower range boundaries being graphed, dosing information is also graphed and detailed via SAS Graph's annotation capability. Further, via html links, the user can 'jump' to a more detailed dosing or lab parameter assessment report.

The ability to link a data point on a graph to a report is a powerful utility and very simply accomplished. In this example the programmer needs only to have three "pieces" in place to have this linking capability. First, an html file named dosing must be housed on the shared network drive under a 'BigAlsWorld' and

'dosing' subdirectory. Next, within the graph program and prior to the plot statement a link variable needs to be established within a data step.

Fig. 6

```
data graphs;
  set graphs;
  glinkme='href=z:\BigAlsWorld\dosing\dosing.html';
run;
```

Then, merely adding a reference to this link as an option in the plot statement provides the desired functionality.

Fig. 7

```
proc gplot data=graphs;
  by ptid parameter;
  plot value*day=measure/
  html=glinkme
  ;

title "Clinical Laboratory Results;
footnote1 j=c height=.8 color=red
"Click on the data point to view the data in a tabular form";
run;
quit;
```

(The phenomenon known as a "programmer's high" should be experienced when a first time SAS/ODS developer sees his/her graph jump to a pre-defined report. For those non-programmers unfamiliar with this phenomenon, imagine the future state of a 'chocoholic' with a fistful of quarters standing in front of a freshly stocked vending machine.)

### Out of Range Lab Graphs

This component's output, including linkages, is very similar to the Pre-Selected Clinical Laboratory graphs. However, the difference here is that subject-level graphs are generated for only those lab parameter that fall above or below normal ranges at any time during the course of the study (including pre-dose and post-dose).

Prior to generating the subject level graphs a descending frequency hbar plot is generated detailing the parameters that fell out of range during the study. This gives the reviewer a quick, generally 'one-page' view of the parameters that may be of concern. The user can then scroll down the Web page and see the specific subjects who had these abnormalities.

This aspect of the application clearly reflects the benefit and intended direction of "Big Al's World". Now, rather than looking through what is often hundreds of pages of printed lab reports, the reviewer can merely scroll through the much smaller subset of lab parameters that fell out of range.

### Average Parameter

Another series of lab graphs are parameter and treatment group specific. For each numeric parameter the reviewer sees the reported mean, minimum, maximum and median measure by study day. This easily allows both trends (mean and median) and outliers (minimum and maximum) to be pictorially assessed.

### Lab Assessment-- "Data Mining"

The last lab component provides the user with the opportunity to "ask" questions about the various sub groups or special populations found within a study. The first portion of the module provides a listing (via Proc Report) of the lab parameters found in the study.

These are then linked to a more detailed parameter-specific report. The detailed report begins by displaying the measures for all of the subjects within the study, day-by-day. Then, as the user

scrolls down the Web page he or she can see descriptive statistics (N, mean, median, range, min, max, standard deviation) by treatment group, sex, race, age group, hormonal status and body mass index group. Group information is also reflected in the subject information so that the user can identify what subjects are contributing to what groups.

### VITAL SIGNS

The vital signs module uses both SAS Graph and the Report procedure and details what happened by subject in terms of blood pressure, temperature, body mass index and heart rate.

#### Graphs

In healthy individuals these measures typically fall into two broad groups. These groups are very simply and non-medically, large and small numbers. Therefore, two graphs are generated for each subject. The first graph (large numbers) holds the blood pressure (supine, sitting and standing) and heart rate. These numbers typically fall into a range between 60 (low heart rate) and 150 (moderately high systolic blood pressure) and small changes should be discernable due to a fairly narrow vertical axis scale.

The second graph would house the smaller numbers that typically fall into a range of around 20 to 40. The measures reported on these subject specific graphs are body mass index and temperature. A body mass index of 19-25 is considered healthy or normal and temperature in Pfizer clinical studies is generally recorded in centigrade. Therefore, a normal 98.6 is recorded as 37.0. Once again this fairly narrow range of measures allow changes that occur during the study to be easily identifiable in picture format.

Finally, much like the clinical laboratory graphs, dosing information is contained via annotations.

#### Reports

For easy comparisons among subjects, via the Report procedure, the reviewer also has the ability to look at all of the study subjects by study day and measure. Further, descriptive statistics by study day are provided for the entire study group and by treatment group to help the reviewer easily identify any trends caused by the new medication.

### SUBJECT SUMMARY (A Better GANTT Chart?)

As of this writing (December, 00) two methods are being evaluated for 'best fit' to provide an overall subject summary. The intent is to provide, via subject specific web pages, all of the clinically important events that occurred during the course of the trial, ranging from study enrollment to termination. The vertical axis on these charts detail the event and the horizontal axis reflects time. Therefore, on a 'single sheet' the reviewer sees Adverse Events, out of range clinical laboratory and vital sign measures, when Physical Exams and ECGs became abnormal, when dosing was administered and when the subject terminated from the study. Further, the symbol function of SAS allows the different events (e.g., AE intensity and duration) to be easily discernable through the use of different colors, shapes and sizes.

At this point it is unclear as to the best SAS-based methodology to provide this functionality. SAS Graph was the initial solution. However, the myriad of data on a single page looked a little cumbersome. The GANTT chart procedure of SAS/OR is now being looked at as a better alternative.

### BENEFIT & NEXT STEPS

As of this writing the user community has agreed that the use of graphics and Web pages can provide benefit in reviewing clinical data. In November 2000 a presentation was made to those physicians and clinical scientists with Early Clinical Development responsibility. The discussion and positive statements generated by a poster presentation on this subject convinced the author that this is a sorely needed utility. The presentation made it clear that

physicians and scientists need timely and easy access to their data without the constraints of learning an elaborate collection of technology.

From a managerial perspective, additional headcount was not added to achieve these goals. Further, user rollout and training generally involved directing the user to a main Web page and letting users "walk through" the various modules. The use of the Web and "pointing and clicking" is now so commonplace that training is essentially limited to explaining what's contained within each of the modules.

Near term plans in "Big AI's World" include continuing to respond to the programming needs of our user community. These needs are currently seen as either adding additional modules to the system or accelerating the speed and frequency by which data becomes available to the application.

Modules that are in progress include graphs for out-of-range vital signs, PK concentration data and QTC data.

Currently, Big AI's World is executed against only those clinical studies that have been completed. It will be advantageous to generate interim runs of these graphs and tables when we have studies that last longer than our typical 3 or 4 weeks. Additionally, this viewable safety information will be extremely useful in determining next steps when conducting dose escalation studies.

### FINDINGS & CONCLUSION

Those experienced with base SAS, SAS Graph, and the Report procedure will find the ODS capability an extremely powerful tool to add to their portfolio of programming techniques. Process-wise, users need only to add a few ODS-type statements to existing SAS graph and report programs to have a functional Web-based reporting system.

Recommended next steps for those unfamiliar with ODS would be to review the SAS samples contained behind the help utility in their Version 8 software and on the SAS Home Page ([www.SAS.com](http://www.SAS.com)). The examples provided on these pages were a significant help to begin programming.

Finally and most importantly, those programmer analyst types who are driven by the pursuit of quality ice cream, good deli, fresh cinnamon scones, or crème brûlée can capitalize on the Output Delivery System's capability and quickly develop very functional and professional web based output. By ("baiting") convincing your clients of the technical difficulty, struggle, and hours worked, "take home" can mean much more than just a paycheck.

### ACKNOWLEDGMENTS

The author wishes to thank those who provided ice cream, encouragement or input into this new system. Including: Dr. Allen Sedman, Dr. D J Dorney, Dr. Ralph Stern, Dr. James Strand, Dr. George Haig, Dr. Candace Bramson, Dr. David Wesche, Mr. Ron Voigtman, Dr. Trevor Mundel, and Mr. Pete Yribar

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# Study: XXXX-XXX

Click on the area you wish to review

## ----- Demographic Data -----

### [Demographic Information](#)

(Graphs including Sex, Race, Study Termination and Hormonal Status)

## ----- Adverse Event Data -----

### [Adverse Event Summary](#)

(AE detail including frequency, time to onset, duration and subject detail)

## ----- Clinical Laboratory Data -----

### [High, Low, and Average Lab Measures](#)

(Numeric lab parameters with detail of screening, high, low and average measures)

### [Clinical Laboratory Assessment](#)

(Lab detail by subject, study, sex, race, hormonal status, age group and body mass index)

### [Therapy Specific Lab Graphs](#)

(Clinician/Physician requested graphs)

### [Out of Range Lab Parameters](#)

(Measures that are above or below normal ranges)

## ----- Vital Signs -----

### [Vital Signs Summary Tables](#)

(Vital Signs by Subject, Study and Treatment Group)

### [Vital Signs Graphs](#)

(Blood pressure & heart rate)

### [Vital Signs Graphs](#)

(Miscellaneous measures (e.g., temperature, body mass index, and respiration))

## ----- Overall Subject Summary -----

### [Summary of Subject Events](#)

(A GANTT chart depicting dosing, Labs, AEs, Physical Exams and ECG results)

Clinical Pharmacology Data Vision--"Big AI's World"			
			<b>Big AI's World.html</b>
Clinical Study	(programmer input)	Clin Pharm Data Vision (CPDV.SAS) Program Oracle Clinical Data Capture: Extract Macros--including ae_in.sas, demo_in.sas, vtl_in.sas, labin.sas, hgt_in.sas, wgt_in.sas	<ul style="list-style-type: none"> <li>9999000.html</li> <li>9999001.html</li> <li>9999002.html</li> <li>9999003.html</li> </ul>
Clinical Area	Macro Executed	Data Provided	Files Created
Adverse Events	aeMENU.sas aeASSESS.sas	Count of AEs by Body System (Proc Report) HBAR of AE Preferred Terms HBAR of AE Duration HBAR of Time to Onset Subject Level Adverse Event Detail (Proc Report)	<ul style="list-style-type: none"> <li>AEASSESS.html</li> <li>— BODY.html</li> <li>— CV.html</li> <li>— DS.html</li> <li>— HAL.html</li> <li>— MAN.html</li> <li>— MS.html</li> <li>— NS.html</li> <li>— RS.html</li> <li>— SS.html</li> <li>— US.html</li> </ul>
Clinical Labs	labMENU.sas labASSESS.sas	Proc Report detailing the numeric lab parameters measured during the study Proc Report detailing lab parameters by subject and descriptive statistics for the study, by sex, race, age group, hormone group, body mass index group	LABASSESS.html
	hiLow.sas	Proc Report detailing all numeric lab parameters. By subject and parameter, the screening measure and high, low and study average is provided.	HiLowAvg.html
	labPARMS.sas	SAS graphs of the clinicians choosing. Lab parameters are chosen based upon the clinicians knowledge of the new medicine and therapy area.	LabPARMS.html
	avgPARAM.sas	Parameter and treatment specific graph detailing minimum, maximum, mean, median values by study day.	AvgPARAM.html
	oRngLABS.sas	SAS graph of any parameter that is out of range during the study	oRngLABS.html
Vital Signs	vsigns1.sas vsigns2.sas	SAS graph by subject that details vital signs and dosing. Proc Report detailing vital signs by subject and descriptive statistics for the study and treatment groups	<ul style="list-style-type: none"> <li>vsigns1.html</li> <li>vsigns2.html</li> </ul>
Subject Summary	gantT.sas	SAS graph or SAS OR Gantt chart detailing the significant or important subjects events that occurred during the course of the study.	subj#.html