Paper 9

ANNOTATED CASE REPORT FORM AUTOMATION SYSTEM

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ABSTRACT

This paper presents an illustration of a SAS®-based annotated Case Report Form (CRF) automation system. SAS macros are used to construct CRF pages from individual data collection modules annotated with database information and to generate an HTML–based viewer system for viewing these assembled, annotated pages. The macros can assemble a number of different annotated modules onto a single CRF page based on user input. This automation system can be used to create a complete set of electronic CRF pages for an entire clinical study, and for the users to review and manage these CRF pages online. The discussion includes topics of:

* Preparing a library of annotated forms and components,
* Providing a SAS macro to construct a CRF page,
* Providing a SAS macro to generate a viewer system,
* Illustrating a pilot CRF automation system.

The SAS products used in this paper are: SAS BASE®, without any limitation of operating systems.

INTRODUCTION

Paper Case Report Forms (CRFs) are used in clinical trials to collect relevant, study related data which is written into the blank fields by investigators or study coordinators. A common practice in the pharmaceutical industry is for a clinical database administrator (CDA) to annotate or mark-up these paper CRF pages which can be composed of several smaller sections or modules. The annotation process involves writing the database file and field names by hand on each of these modules so that anyone who needs access to the data will have a clear path to its' location. The CDA then distributes the annotated CRF hardcopies to study team members and other interested parties. This is a manual and time-consuming process.

To alleviate the tedium of this manual process an automated system to create electronic, annotated CRF pages for any clinical study was developed. Reuse of existing or previously annotated CRF modules is a key component of the system. This approach assumes that all existing CRF forms or modules exist in annotated format and are stored in a library. Examples of frequently used modules or pages include the following: Adverse Experience, Significant Medical/Surgical History and Physical Examination, Prior / Concomitant Medication, etc. The automation system allows the CDA to select the annotated CRF modules in the library by passing parameters to the system, which then assembles the selected modules into one Web-based CRF page. The second SAS macro in the automation system will collect all CRF pages together for a study and provides the capability of viewing the annotated CRF on line.

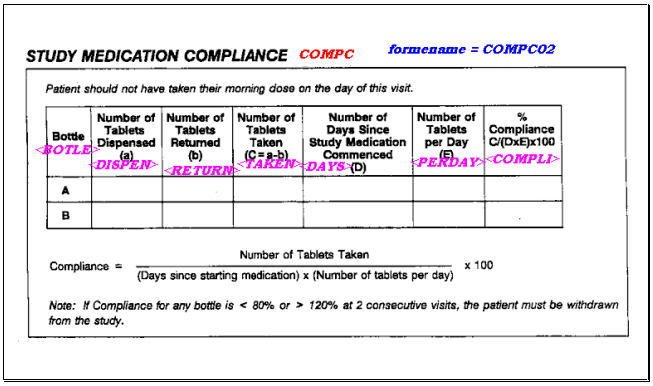
The viewer system provides a central depository with document version control and fast electronic document delivery for all annotated CRF pages for any protocol. The system will eliminate the need to re-annotate the CRF when a new study starts Two SAS macros are provided for the creation of one single annotated CRF page. Another macro creates a viewer system for the whole CRF pages for a study.

LIBRARY FOR STANDARD FORMS

A library, in which all annotated standard forms and components are kept, is established first. This process involves the following steps:

Step 1: Scan all CRF forms and components, and
save them as electronic files with gif format,
Step 2: Annotate each form and store it in the library.

The following figures are samples of annotated forms in the library.


STUDY MEDICATION COMPLIANCE COMPC formename = COMPC02

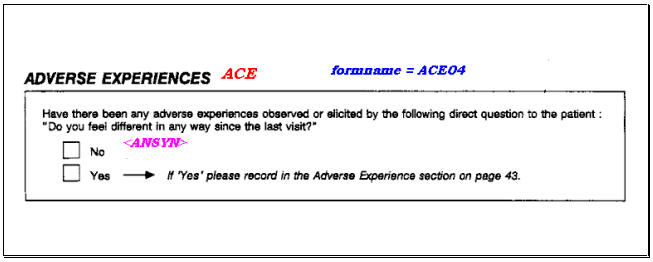
Patient should not have taken their morning dose on the day of this visit.

Bottle <BOTLE>	Number of Tablets Dispensed (a) <DISPEN>	Number of Tablets Returned (b) <RETURN>	Number of Tablets Taken (C = a-b) <TAKEN>	Number of Days Since Study Medication Commenced (D) <DAYS>	Number of Tablets per Day (E) <PERDAY>	% Compliance C/(DxE)x100 <COMPLI>
A						
B						

Compliance = Number of Tablets Taken / (Days since starting medication) x (Number of tablets per day) x 100

Note: If Compliance for any bottle is < 80% or > 120% at 2 consecutive visits, the patient must be withdrawn from the study.

Figure 1. Sample of Annotated Compliance Form

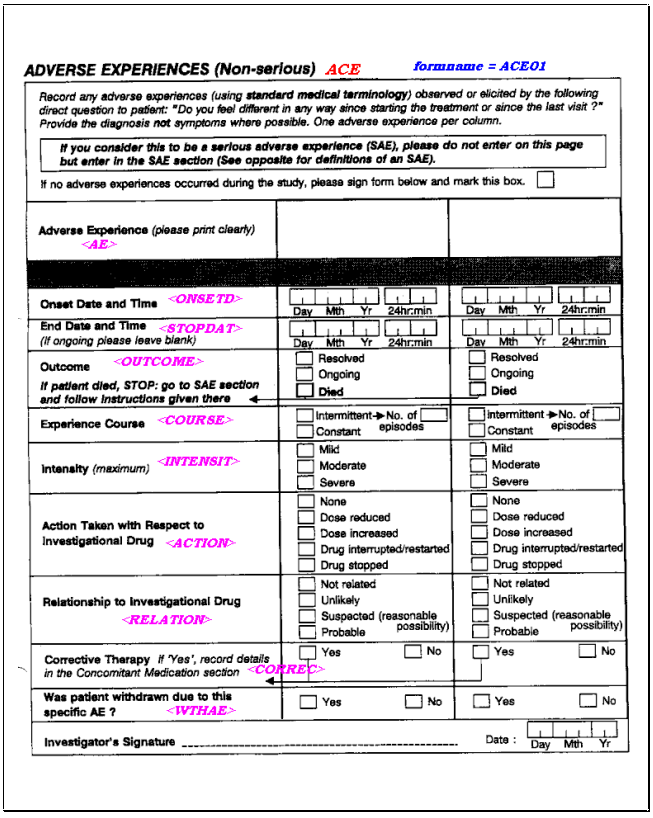

ADVERSE EXPERIENCES ACE formname = ACE04

Have there been any adverse experiences observed or elicited by the following direct question to the patient : "Do you feel different in any way since the last visit?"

☐ No <ANSYN>

☐ Yes → If 'Yes' please record in the Adverse Experience section on page 43.

Figure 2 Sample of Annotated AE Form


ADVERSE EXPERIENCES (Non-serious) ACE formname = ACE01

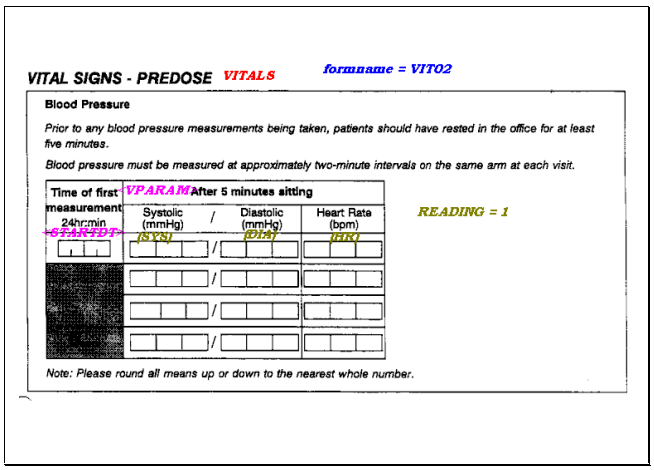
Record any adverse experiences (using **standard medical terminology**) observed or elicited by the following direct question to patient: "Do you feel different in any way since starting the treatment or since the last visit ?" Provide the diagnosis not symptoms where possible. One adverse experience per column.

If you consider this to be a serious adverse experience (SAE), please do not enter on this page but enter in the SAE section (See opposite for definitions of an SAE).

If no adverse experiences occurred during the study, please sign form below and mark this box. ☐

Adverse Experience (please print clearly) <AE>		
Onset Date and Time <ONSETD>	Day Mth Yr 24hr:min	Day Mth Yr 24hr:min
End Date and Time <STOPDAT> (If ongoing please leave blank)	Day Mth Yr 24hr:min	Day Mth Yr 24hr:min
Outcome <OUTCOME> If patient died, STOP: go to SAE section and follow instructions given there	☐ Resolved ☐ Ongoing ☐ Died	☐ Resolved ☐ Ongoing ☐ Died
Experience Course <COURSE>	☐ Intermittent → No. of episodes ☐ Constant	☐ Intermittent → No. of episodes ☐ Constant
Intensity (maximum) <INTENSIT>	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Action Taken with Respect to Investigational Drug <ACTION>	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped	☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug interrupted/restarted ☐ Drug stopped
Relationship to Investigational Drug <RELATION>	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable	☐ Not related ☐ Unlikely ☐ Suspected (reasonable possibility) ☐ Probable
Corrective Therapy If 'Yes', record details in the Concomitant Medication section <CORREC>	☐ Yes ☐ No	☐ Yes ☐ No
Was patient withdrawn due to this specific AE ? <WITHAE>	☐ Yes ☐ No	☐ Yes ☐ No
Investigator's Signature _____	Date : Day Mth Yr	

Figure 3 Sample of Annotated AE Form


VITAL SIGNS - PREDOSE VITALS formname = VIT02

Blood Pressure

Prior to any blood pressure measurements being taken, patients should have rested in the office for at least five minutes.

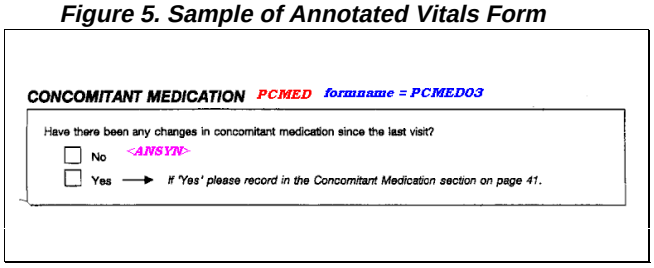
Blood pressure must be measured at approximately two-minute intervals on the same arm at each visit.

Time of first measurement 24hr:min <STARTDT>	VPARAM After 5 minutes sitting Systolic (mmHg) (SYS) / Diastolic (mmHg) (DIA)	Heart Rate (bpm) (HR)
	/	
	/	
	/	
	/	

READING = 1

Note: Please round all means up or down to the nearest whole number.

Figure 5. Sample of Annotated Vitals Form


CONCOMITANT MEDICATION PCMED formname = PCMED03

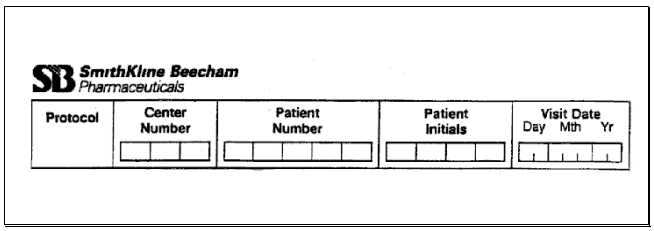
Have there been any changes in concomitant medication since the last visit?

☐ No <ANSYN>

☐ Yes → If 'Yes' please record in the Concomitant Medication section on page 41.

Figure 4. Sample of Annotated CC Med Form

Each CRF page contains a header portion, which contains sponsors or protocol information. This is also stored in the library. The page header is shown below:


SB SmithKline Beecham Pharmaceuticals

Protocol	Center Number	Patient Number	Patient Initials	Visit Date Day Mth Yr

Figure 6. Page Header

SAS MACRO FOR ASSEMBLING A CRF PAGE

The two parts of the CRF page are the generic portion and the protocol specific text or instructions. The generic portion is the area in which CRF standard forms and page header are selected from the library and are assembled as part of CRF page. The protocol specific portion is the area that the SAS macro allows the CDA to put study related messages, text, or instructions into a CRF page.

The following SAS macro allows the CDA to select up to 5 standard forms and/or components from the library and put a message or text to construct a CRF page.

```
%macro apage ( pg=, cpg=, modul=, c1=, m1=, c2=,
               m2=, c3=, m3=, c4=, m4=, c5=, m5=);
```

```
  %LET H1 ='<HTML><HEAD></HEAD><BODY BACKGROUND=
whiteb.gif><IMG SRC=pghead.gif><BR>';
  %let H11 = '<HR>';
  %LET H2A = '<PRE><H2>';
  %let h2B = '</PRE></H2>';
  %LET H2 ='</BODY></HTML>';

data _null_;
 file "pg&prot.&pg..htm";
 if _n_ = 1 then put @1  &H1  &H2A /;
     PUT &cpg    /;
     PUT &h2B &H11;
    %if &modul = 1 %then %do;
      put &c1  '</PRE></H3>';
      put "<IMG SRC=&m1..gif>";
      put @1 &h2;
    %end; %else
    %if &modul = 2 %then %do;
      put  &H2A &c1 &H2B ;
      put "<IMG SRC=&m1..gif><BR>";
      put  &H2A &C2 &H2B;
      put "<IMG SRC=&m2..gif>";
      put @1 &h2;
%end; %else
%if &modul = 3 %then %do;
     put &H2A &c1 &H2B;
     put "<IMG SRC=&m1..gif><BR>";
     put &H2A &C2 &H2B;
     put "<IMG SRC=&m2..gif><BR>";
     put &H2A &C3 &H2B;
     put "<IMG SRC=&m3..gif>";
     put @1 &h2;
%end; %else
%if &modul = 4 %then %do;
     put &H2A &c1 &H2B;
     put "<IMG SRC=&m1..gif><BR>";
     put &H2A &C2 &H2B;
     put "<IMG SRC=&m2..gif><BR>";
     put &H2A &C3 &H2B;
     put "<IMG SRC=&m3..gif>";
     put &H2A &C4 &H2B;
     put "<IMG SRC=&m4..gif>";
     put @1 &h2;
%end; %else
%if &modul = 5 %then %do;
     put  &H2A &c1 &H2B;
     put "<IMG SRC=&m1..gif><BR>";
     put  &H2A &C2 &H2B;
     put "<IMG SRC=&m2..gif><BR>";
     put &H2A &C3  &H2B;
     put "<IMG SRC=&m3..gif>";
     put &H2A &C4 &H2B;
     put "<IMG SRC=&m4..gif>";
     put &H2A &C5 &H2B;
     put "<IMG SRC=&m5..gif>";
     put @1 &h2;
%end; run;
%mend;
```

The arguments for the SAS macro ***apage*** are:

pg: page number,
cpg: non-generic message text for this page,
modul: number of standard forms in this page,
c_i: message text for ith standard form,
m_i: ith standard form image file name.

The parameter module ranges from 1 to 5. The *i* subscript in ci and mi depends on parameter module and also ranges from 1 to 5. The following example selects two standard forms, cc001 and ae001 from the library and parameters pg and cpg are assigned respectively as 1 and SB223030/999 .

```
%apage (pg = &pg, cpg = " &drug./&prot
SCREEN VISIT   PAGE 1", modul= 2,
   c1 = %str('OBS = 1010.PRE'), m1=cc001,
   c2 =, m2 = ae001,
   c3 =, m3= , c4 = ,m4=, c5 = ,m5=);
```

A CRF page is assembled by this macro and shown in Figure 7. This sample CRF page starts with the page header and consists of 2 standard forms: Concomitant Medication with file name of cc001 and Adverse Experinces with file name of ae001. It also includes non-generic text input by the GDM, such as: compound number, study number, page number, visit, and observation code.

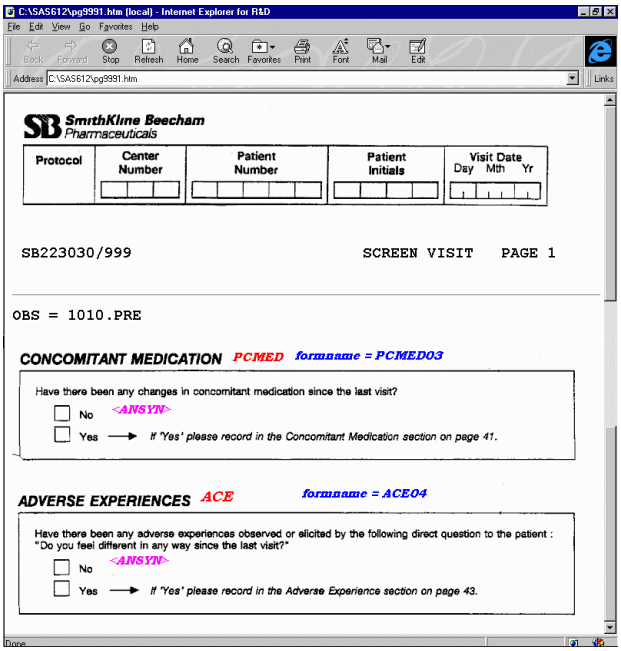


Figure 7. A Sample CRF page assembled by SAS macro

SAS MACRO FOR VIEWER SYSTEM

A viewer is a system to browse, link and display individual CRF pages. The system consists of two components: 1) a menu screen with a list of CRF page description from which the user can make a selection, 2) display of selected CRF pages. The following sections will discuss the SAS macro for viewer system in detail. This is a pilot and feasibility study; the dummy protocol

999 consists of five CRF pages. The macro ***viewer*** is flexible and can be modified easily for any number of CRF pages.

The arguments for this SAS macro ***viewer*** are:
ofile: HTML file and where to store it,
drug: compound name,
prot: protocol number,
npage: number of pages in the system.

```
%macro viewer(ofile=, drug=,prot=,npage=);
  %let drug = &drug;
  %let H1A ='<HTML><HEAD></HEAD><BODY
BACKGROUND=sb2.gif><IMG SRC=scroll.gif><BR>';
  %let H1B ='<IMG SRC=blackba1.gif><H2><FONT
COLOR="RED">CRF PAGE CONTENTS FOR<BR>';
  %let H3C=" &drug </FONT>Protocol: &prot";
  %let H4B='</H2><BR>';
  %let LSTART =%STR('<A HREF=');
  %let LLABEL ='>';
  %let LEND   ='</A><BR>';
  %let H5 ='</BODY></HTML>';
  %inc 'apage.sas';
  %let pg = 1;
%apage(pg = &pg, cpg=" &drug./&prot
SCREEN VISIT   PAGE 1", modul= 2,
  c1 = %str('OBS = 1010.PRE'), m1 = cc001,
  c2 =, m2 = ae001,
  c3 =, m3 = , c4 =, m4 = ,
  c5 =, m5 =  );
%let HL1 ='"PG9991.HTM"';
%let HT1 ="PAGE 1 ACE AND CC";
%let pg = 2;
%apage( pg = &pg, cpg = "&drug./&prot
SCREEN VISIT   PAGE 2", modul= 1,
  c1 = ,m1 = AEN001 ,
  c2 =, m2 = ,
  c3 =, m3 = , c4 =, m4 = ,
  c5 =, m5 =  );
%let HL2 ='"PG9992.HTM"';
%let HT2 ="PAGE 2 NON SAE";
%let pg = 3;
%apage( pg = &pg, cpg = " &drug./&prot
RUN IN VISIT   PAGE 3"modul =  1
  c1 = ,m1 = comp001 ,
  c2 =, m2 = ,
  c3 =, m3 = , c4 =, m4 = ,
  c5 =, m5 =  );
%let HL3 ='"PG9993.HTM"';
%let HT3 ="PAGE 3 COMPLIANCE";
%let pg = 4;
%apage( pg = &pg, cpg = " &drug./&prot
RUN IN VISIT    PAGE 4", modul=  1  ,
c1 = ,m1 = stm001 ,
  c2 =, m2 = ,
  c3 =, m3 = , c4 =, m4 = ,
  c5 =, m5 =  );
%let HL4 ='"PG9994.HTM"';
%let HT4 ="PAGE 4 STUDY MEDICATION";
%let pg = 5;
%apage( pg = &pg, cpg = "&drug./&prot
RUN IN VISIT  PAGE 5", modul = 1,
  c1 = ,m1 = preds001 ,
  c2 =, m2 = ,
  c3 =, m3 = ,
  c4 =, m4 = ,
  c5 =, m5 =  );
%let HL5 ='"PG9995.HTM"';
%let HT5 ="PAGE 5 PRE DOSE VITAL SIGNS";

data _null_;
   file " &ofile";
   put @1  &H1A &H1B  ;
   put @1   &H3C &H4B;
     %DO I = 1 %TO &NPAGE;
   put &LSTART &&HL&I &LLABEL &&HT&I &LEND;
     %END;
   put @1   &H5 ; run;
%mend;
```

The following example shows how to invoke ***viewer*** macro.

```
%viewer(ofile = CRF999.HTM,
        drug = SB223030,
        prot = 999,
        npage = 5);
```

This example creates a VIEWER system HTML file with file name of CRF999.HTM. The resulting CRF999.HTM file can be opened as a local file from the user's browser or placed on the Web server and referenced by its URL (uniform resource locator).

The following figures show the illustrated VIEWER system menu selection page. When the user selects a CRF page, the corresponding CRF image will be displayed. For example, Figure 9 will be displayed after a selection of 'PAGE 4 STUDY MEDICATION' from the menu screen. The users can get a hardcopy of the CRF pages by using browser's print utility.

Figure 8. CRF Viewer Menu Selection Screen

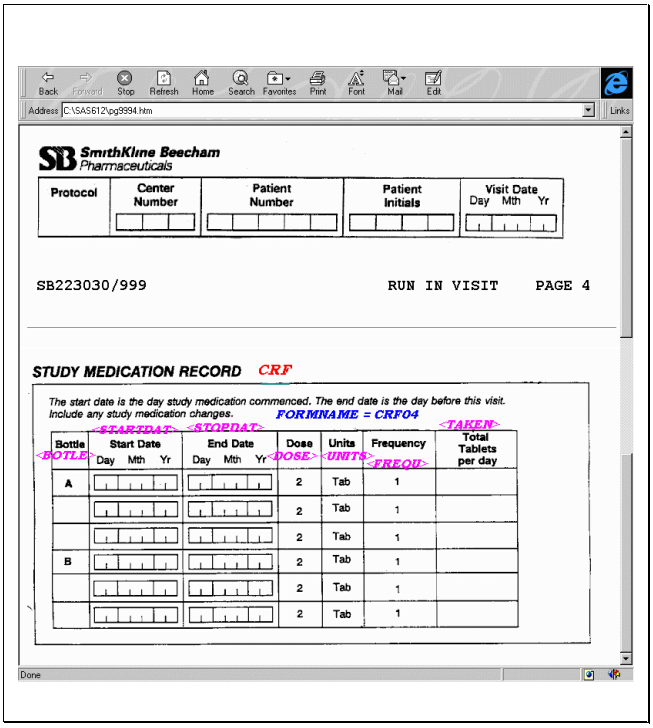


Figure 9. Display of Study Medication Page

CONCLUSION

This paper describes a feasibility study for an Annotated CRF Automation System. The findings from this pilot study are:

* compliance of company's policy of reusing standard forms,
* reduction of the CDAs annotation efforts, which reduces the tedium of the manual process
* a centralized depository for CRF document management ,
* increased online accessibility and effeciency of annotated CRF distribution.

REFERENCES

[1] Shi-Tao Yeh,:*SAS Software G3D Animation and Graphic Viewer System,* SUGI 23, SAS Users Group International Conference Proceedings, pp. 1162-1165, March 1998

[2] Shi-Tao Yeh,:*SAS Output Viewer System ,* NESUG '97 Annual Conference Proceedings, pp. , October 1997

[3] Shi-Tao Yeh and Andrew Yeh,:*Exporting SAS Output onto the World Wide Web,* SUGI 22, SAS Users Group International Conference Proceedings, pp. 1040-1044, March 1997

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