Paper PS21

CLIREV
A friendly and flexible Clinical Data Review Tool

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ABSTRACT
As a small cooperative group in oncology working with many companies, each one with different size and methodologies, we have to continuously adapt our systems and, in certain circumstances, our processes, to the different company requirements.
We therefore developed a SAS® Clinical Data Review Tool in which data are periodically loaded from a number of different clinical databases and data structures. While the structure of each clinical database is tailored as much as possible to comply with the individual company standards, the 'data-review' tool provides standardised reports for all SENDO personnel who need to have access to the clinical data.
These standard reports range from individual patient or panel listings (data-dump) to patient profiles and ad-hoc reports for safety and efficacy data review. In addition basic statistics for both administrative data (e.g.CRFs tracking) and clinical data (e.g. adverse events) are made available.
CLIREV (CLInical data REView) is an intranet system periodically and automatically updated from which clinical study data can be easily accessed trough the browser.
Future developments of CLIREV are planned to be more compliant with current CDISC terminology; moreover, although these reports are frequently and automatically updated in order to reflect the actual current database contents as much as possible, they are 'static' outputs and therefore we wish to implement some functionality for ad-hoc queries.

INTRODUCTION
During the last decade many pharmaceutical industries have been revising their clinical development processes and tools with the main aim of optimizing the clinical development phase and thereby reduce its duration and costs. One of the critical areas identified is data management and one of the solutions widely adopted consists of standardization of data collection and handling tools.
As a consequence, SENDO has been requested more and more to comply with a number of different requirements from the industries, resulting in different data collection supports (paper CRFs, remote data-entry) and different database systems and structures. The heterogeneity of the row data and the lack of user-friendly and flexible browsers have progressively become a major hindrance for SENDO personnel reviewing clinical data.
The main need expressed by these end-users was to have a quick and easy access to the clinical data, with the possibility to choose among different report formats such as full data listings, simple tables summarizing the main study data and individual patient summaries (patient profiles). More specifically, these outputs had to have standardized layouts and structures; key variables had to be copied or moved from their original place in the database and added to different sections to facilitate the detection of protocol violations and inconsistencies across visits and forms; some calculated variables (e.g., laboratory results converted into their SI units; intervals between treatment cycles) had to be included to avoid manual calculations and provide at glance fit-for-use information; some administrative data (e.g., CRFs tracking) had to be continuously available for monitoring the data collection progress.
The system developped to satisfy these needs, called CLIREV (CLInical data REView), is an intranet system periodically and automatically updated from which clinical study data can be easily accessed trough the browser.

DATA ORGANISATION AT SENDO
Clinical Data at SENDO are managed with two main systems:

- AcesWin® by Theradex (remote and central data-entry)
- ClinTrial™ by PhaseForward (central data-entry only)

Data are managed in most cases by means of paper CRF; however for some studies (especially Phase I studies), data are directly collected in electronic format at the Investigator Site and periodically transferred to SENDO Head Quarter.
Regardless of the type of solution adopted for data collection, data are periodically extracted and loaded onto SAS, so that a sort of data-warehouse of all the studies managed at SENDO can be maintained. Following the data-load onto SAS, a set of automatic reports are generated and published onto the SENDO Intranet (figure 2 and 3).

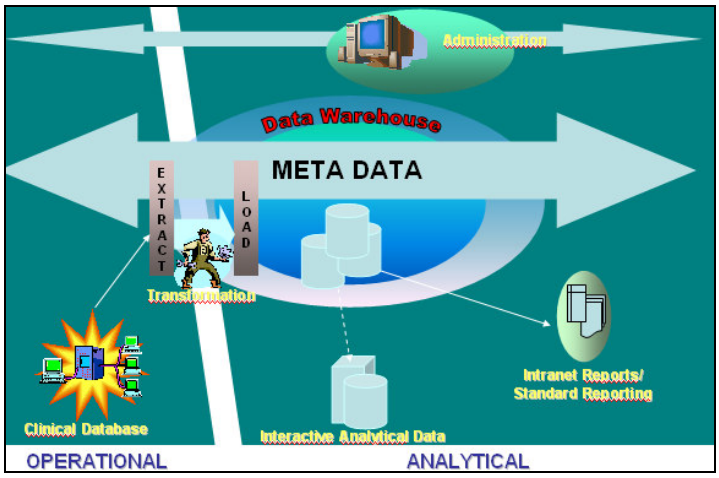


Figure 1: Clinical Data Process at SENDO

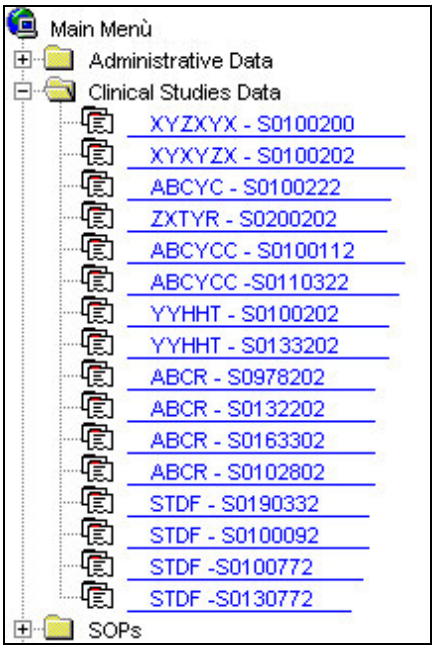


Figure 2: SENDO Trials

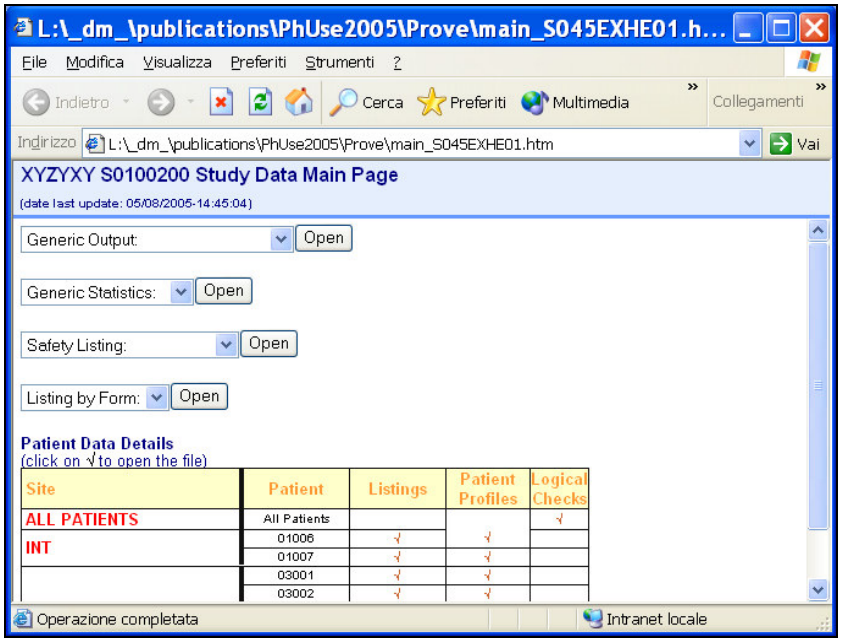


Figure3: Study Intranet Main Page

TYPE OF REVIEW TOOL

Over the years, and as a continuous development process, SENDO has developed a number of different types of review tools (reports). These can be divided into administrative, data listings, patient profiles and special reports (all these reports are customizable trough a set of SAS macro routines). In addition for each study it is possible to define specific ad-hoc reports upon the requests of the Study Team.

ADMNISTRATIVE REPORTS

Administrative reports are tools to review both the accuracy of the data when automatic systems are used to populate derived variables (e.g. Coding Statistics and Centralized Laboratory Conversion for hematology and chemistry) and the completeness of the information (CRF Tracking, see figure 4).

DATA-DUMP LISTINGS

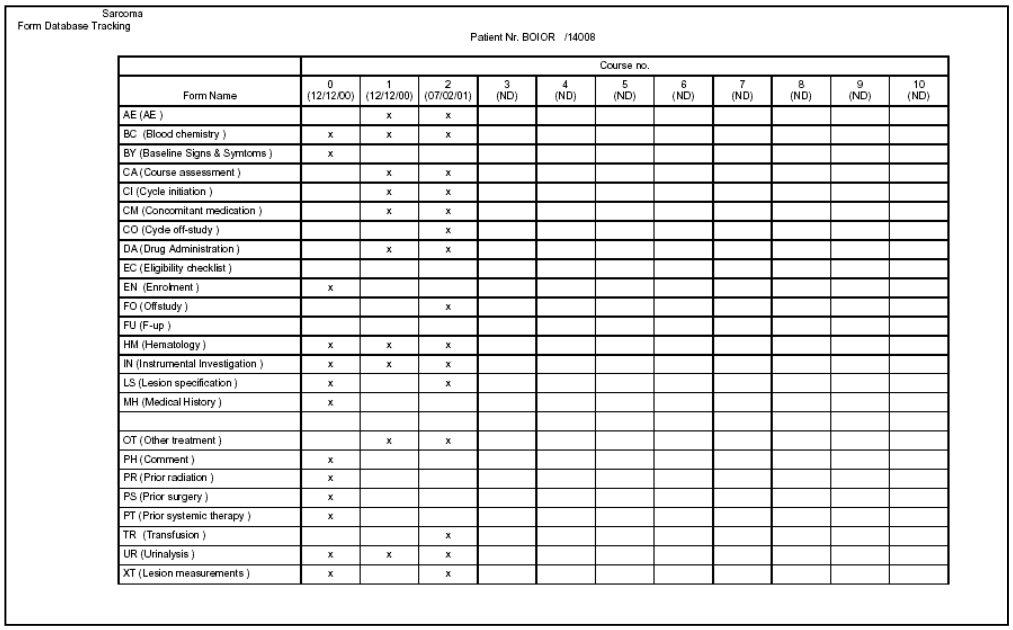
These are simple listings (scratch listings) of all database contents and they report data as they are entered onto the clinical database; they are useful for a quick data view.

PATIENT PROFILES

Patient profile, also known as individual case summary or case report form tabulation, is a useful tool to review data from an individual patient/subject during a study (figure 5). They offer an opportunity to have a complete picture of the patient/subject status, so that problems can be easily addressed:

- Clinical questions such as specific adverse event preceded by warning sings in related parameters
- From the data-management point of view, 'rules' such as "Concomitant medications used to treat adverse events should have been administered soon after onset of the event and stopped near the resolution date for

that adverse event" are hard to address with programming queries since they involve complex relationships between multiple data values for each patient and are fairly open-ended without precise definitions

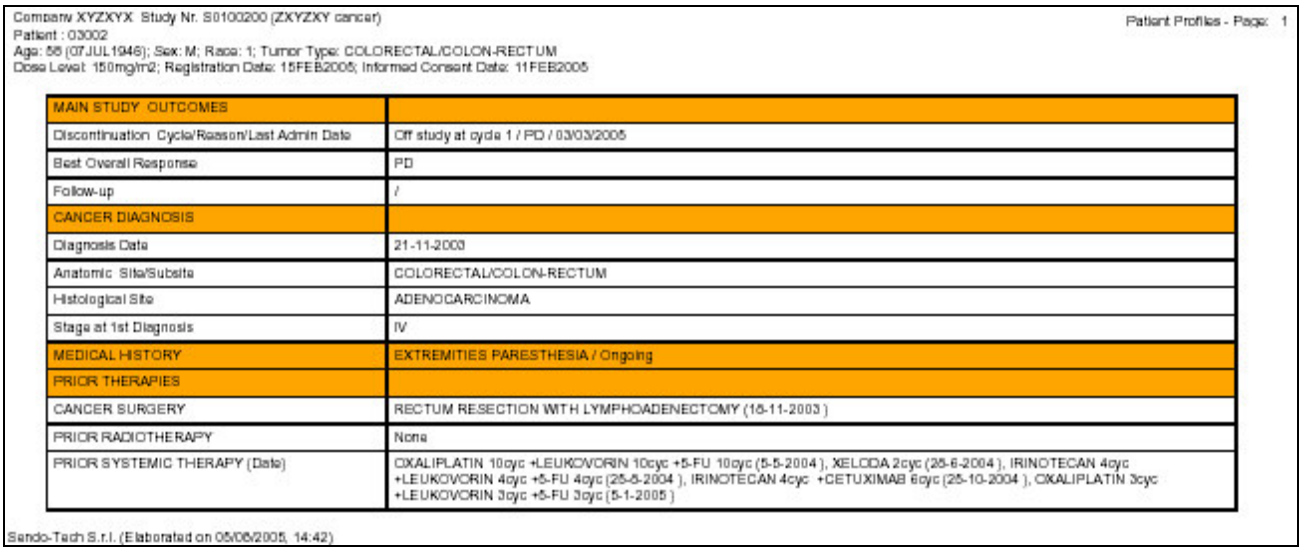


Sarcoma
Form Database Tracking

Patient Nr. BOIOR /14008

	Course no.										
Form Name	0 (12/12/00)	1 (12/12/00)	2 (07/02/01)	3 (ND)	4 (ND)	5 (ND)	6 (ND)	7 (ND)	8 (ND)	9 (ND)	10 (ND)
AE (AE)		x	x								
BC (Blood chemistry)	x	x	x								
BY (Baseline Signs & Symtoms)	x										
CA (Course assessment)		x	x								
CI (Cycle initiation)		x	x								
CM (Concomitant medication)		x	x								
CO (Cycle off-study)			x								
DA (Drug Administration)		x	x								
EC (Eligibility checklist)											
EN (Enrolment)	x										
FO (Offstudy)			x								
FU (F-up)											
HM (Hematology)	x	x	x								
IN (Instrumental Investigation)	x	x	x								
LS (Lesion specification)	x		x								
MH (Medical History)	x										
OT (Other treatment)		x	x								
PH (Comment)	x										
PR (Prior radiation)	x										
PS (Prior surgery)	x										
PT (Prior systemic therapy)	x										
TR (Transfusion)			x								
UR (Urinalysis)	x	x	x								
XT (Lesion measurements)	x		x								

Figure 4: CRF Tracking



Company XYZXYX Study Nr. S0100200 (ZXYZXY cancer)
Patient : 03002
Age: 58 (07JUL1946); Sex: M; Race: 1; Tumor Type: COLORECTAL/COLON-RECTUM
Dose Level: 150mg/m2; Registration Date: 15FEB2005; Informed Consent Date: 11FEB2005

Patient Profiles - Page: 1

MAIN STUDY OUTCOMES	
Discontinuation Cycle/Reason/Last Admin Date	Off study at cycle 1 / PD / 03/03/2005
Best Overall Response	PD
Follow-up	/
CANCER DIAGNOSIS	
Diagnosis Date	21-11-2003
Anatomic Site/Subsite	COLORECTAL/COLON-RECTUM
Histological Site	ADENOCARCINOMA
Stage at 1st Diagnosis	IV
MEDICAL HISTORY	EXTREMITIES PARESTHESIA / Ongoing
PRIOR THERAPIES	
CANCER SURGERY	RECTUM RESECTION WITH LYMPHOADENECTOMY (18-11-2003)
PRIOR RADIOTHERAPY	None
PRIOR SYSTEMIC THERAPY (Date)	OXALIPLATIN 10cyc +LEUKOVORIN 10cyc +5-FU 10cyc (5-5-2004), XELODA 2cyc (25-6-2004), IRINOTECAN 4cyc +LEUKOVORIN 4cyc +5-FU 4cyc (25-8-2004), IRINOTECAN 4cyc +CETUXIMAB 6cyc (25-10-2004), OXALIPLATIN 3cyc +LEUKOVORIN 3cyc +5-FU 3cyc (5-1-2005)

Sendo-Tech S.r.l. (Elaborated on 05/05/2005, 14:42)

Figure 5: Patient Profile

SPECIAL REPORTS

Special reports for better managing safety and efficacy are also available as a standard tool.

As a group working in early clinical oncology development, one of the primary endpoints is Tumor Response. The Evaluation of such endpoint is derived from multiple and repeated evaluations of the tumor across the study period; the determination of the response (i.e. disappearance of tumor lesions or quantification of any changes in their size), is determined by the sum of diameter size of each tumor lesion at each assessment [1]. The special report for tumor response evaluation (figure 6), is a mix of information pulled from different panels/forms, study periods and derived (calculated) variables.

OTHER REPORTS

Other ad-hoc reports can be produced if planned with the Study Team and once developed and tested, they can be put in the production loop.

SIMPLE STATISTICS

These are simple statistics to monitor patient accrual, off-study reasons and main safety outcomes.

Company XYZXYX
Study Nr. S0100200 (ZXYZXY cancer)
Patient Nr. 01004 / GD SOFT_TISSUE_SARCOMA

Response Evaluation

Page No. 1

First Drug administration: 23/11/2000

	Baseline	CYCLE 1	CYCLE 2	CYCLE 3	CYCLE 4	CYCLE 5	CYCLE 6	CYCLE 7	CYCLE 8	CYCLE 9
Drug Administration Date		23/11/2000	15/12/2000	16/01/2001	06/02/2001					
Last Assessment Date	23/11/2000		28/12/2000		23/02/2001					
Months from treatment start	0		1.2		3					
TARGET (measurable)										
1 - NODULAR LESION (UPPER RIGHT LUNG)	{23NOV00} 1 (CTSCAN)		{28DEC00} (CTSCAN)		{23FEB01} (CTSCAN)					
2 - NODULAR LESION (LOWER RIGHT LUNG)	{23NOV00} 1 (CTSCAN)		{28DEC00} (CTSCAN)		{23FEB01} (CTSCAN)					
3 - NODULAR LESION (LEFT LUNG)	{23NOV00} 1 (CTSCAN)		{28DEC00} (CTSCAN)		{23FEB01} (CTSCAN)					
4 - LEFT PELVIS MASS	{23NOV00} 10 (CTSCAN)		{28DEC00} 10 (CTSCAN)		{23FEB01} 12.5 (CTSCAN)					
Sum of Diameters	13		10		12.5					
Diff. from baseline (%)			-23.1		-3.8					
Diff. from nadir (%)			-23.1		25					
NON-TARGET (non-measurable)										
NEW LESIONS										
OVERALL RESPONSE										
Investigator		NT	SD	NT	PD					
Calculated			SD		PD					
OFF STUDY	Yes									

Figure 6: Tumor Response Evaluation

TECHNICAL DETAILS

CLIREV has been developed using SAS/BASE®, SAS/STAT® and SAS/GRAPH® modules.
In the following sections, some of the main relevant technical aspects of CLIREV are presented.

FOLDERS AND FILES ORGANISATION

At the basis of the CLIREV, is the standardization of folders and files (also regulated by a Standard Operating Procedure). Across Companies, Compounds and Studies, a standard folders and files organization is maintained. This organization has a key-role in the automation of the entire process (see a model in figure 7).

AUTOMATIC PROCESS FOR DATA LOAD AND REPORT GENERATION

The core of CLIREV is a SAS job with a macro routine generating an infinite loop. Within the loop, SAS processes the list of active studies and checks for any available update (data extraction). Once an update is found, SAS selects the appropriate study main program (_INTRANET.SAS) and processes it.

```
%MACRO AUTO;
   ***Infinite Loop;
   %DO %WHILE(0=0);
        ***Check Active Studies and Get Nr. of Studies;
        %ACTIVESTU;
        ***Loop trough the Active Studies;
        %DO STUNR=1 %TO &NSTU;
            ***Get Study Info, such as data, program and output path;
            <……More Code……>
            ***Check for any Specific Study Update;
            %ANYUPD(STUNR=&STUNR);
            ***If any update run process for selected study (&ANYUPD);
            %IF &ANYUPD eq YES %THEN %DO;
                %INCLUDE "&PATHDATA.\prg\_INTRANET.SAS";
            %END;
        %END;
        ***Wait for 30 seconds;
        data _null_;
          rc=sleep(30);
        run;
   %END;
%MEND AUTO;
```

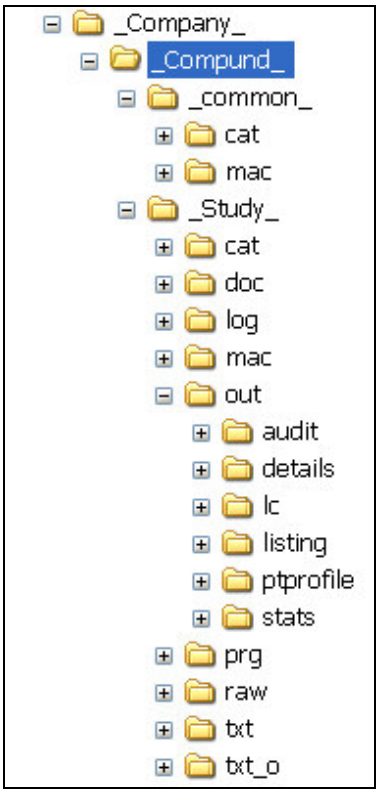


Figure 7: Model for Folders and Files Organization

At any time the administrator of the system and the data-manager can check the status of the job (figure 8).

_INTRANET.SAS

Once a study has been set-up (protocol, CRFs, clinical database, etc.) the definition of the SAS clinical database structure and reporting system can start. For each study a SAS main program called _INTRANET.SAS is then created, onto which the specific CLIREV steps are defined (figure 9).

Thanks to the standardization of SAS clinical database structure and the availability of a library of macro routines for standard reporting, the set-up of a study in CLIREV does not take more than a week for the implementation of the standard functionalities.

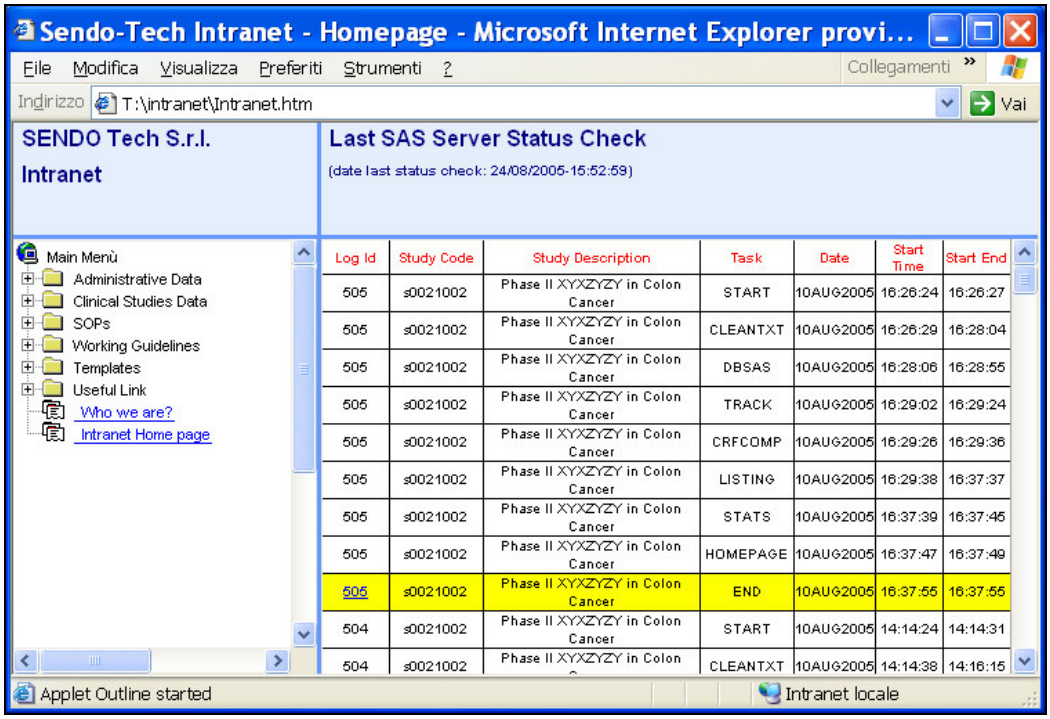


Figure 8: CLIREV Monitoring

```
%*-------------------------------------------------------------------------
General Setting
-------------------------------------------------------------------------;
***Path of Study in the data-management area (&DRIVE is defined elsewhere);
%LET PATHST=&DRIVE./XYX/YXSR/&CODE;
%LET CODE=s0021002;

***Program;
filename prg "&PATHST./prg";

***Library;
libname db "&PATHST./raw";
libname library "&PATHST./cat";

%*-------------------------------------------------------------------------
Output Setting
-------------------------------------------------------------------------;
option pageno=1 nodate missing=" " papersize="ISO A4" orientation=LANDSCAPE;
ods listing close;
%TEMP(STYLENAM=DefaultNew,     STYLEPAR=Styles.Default,
      FONT="Helvetica, Arial", SIZE=8pt);

%*-------------------------------------------------------------------------
Execute Step by Step DM Procedures
-------------------------------------------------------------------------;
***Data Load;           %inc prg(_DBSAS);
***CRF Tracking;        %inc prg(_TRACK);
***Data Dump Listings;  %inc prg(_LISTING);
***Patient Profiles;    %inc prg(_PTPROFILE);
***Response Evaluation; %inc prg(_RESPONSE);
***Ad-hoc Reports;      %inc prg(_DETAIL);
***Statistics;          %inc prg(_STATS);
***Intranet Homepage;   %inc prg(_HOMEPAGE);

ods listing;
```

Figure 9: Example of study _INTRANET.SAS

CONCLUSION

The CLIREV project started in 2003 and is continuously under development with the improvement of existing tools and the creation of new tools for better data review.

Users at SENDO (data-manager, CRA, trial manager and clinical scientist) have now a unique system to be accessed for data review regardless of the clinical database used and the specific company requirements for database design.

The simplicity of its technical design (e.g. use of basics SAS modules, no specific third-party software installation required), allows an easy maintenance and update of each component.

Although CLIREV is developed following SENDO policies and within its specific contents, some of the idea and some of the technical solutions adopted, can be considered a good example for implementing a similar solution within other organizations.

REFERENCES

1. Therasse P. et al. New Guidelines to Evaluate the Response to Treatment in Solid Tumors. Journal of National Cancer Institute 2000; 92(3): 205-216

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

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