Paper TT02

Digitalization of Clinical Study Report (CSR) Tables and Listings for Cross-Report Verification

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ABSTRACT

Large-scale efficacy clinical trials generate numerous table and listing reports in PDF or MS-Word format for inclusion in Clinical Study Reports. The importance of data accuracy, frequency of generation and sheer length of reports combined, make their verification crucial, time-consuming, and prone to human error. This paper presents the framework and one of the tools we have developed at Bayer to automate a number of verification checks that help improve the quality of our TLF deliverables by performing various consistency checks for every study deliverable. This is done by digitalizing and storing the contents of the reports to a standardized cell-based data repository with each cell stored having multiple properties associated with it. We present specific examples of our tool using mock data from a Phase III clinical trial study and show the benefits such a tool can have in improving the quality of the deliverables.

INTRODUCTION

Over last 10 years, the number of Tables, Listings & Figures (TLFs) have grown exponentially for our Clinical Study Reports. As the demand for our TLFs grow and timelines to provide these TLFs to our study teams shrink, the probability of human error increases tremendously. Not to mention that quality checking Tables and Listings visually for discrepancies is tedious, boring and time-consuming task. In this paper we will show you how to automate checking for certain discrepancies in our TLFs package; how to take your previous studies, or your ongoing studies, and quickly identify existing discrepancies.

These checks will:

- Compare results across reports to identify inconsistencies within analyzed counts.
- Look for consistency of big ‘N’ for a given population.
- Locate program file, log files and outputs for a study.
- Check program code for pre-defined typical problems/errors.
- Scan program log for critical messages such as errors & warnings.
- Analyze program output, titles and footnotes.
- Display quality check results in comprehensive, readable form.
- Verification & Documentation from these checks can be implemented as part of your validation process.
- Have flexibility to keep adding new checks to improve the quality of your TLFs package.

GENERAL FRAMEWORK

To identify discrepancies in Table and Listing reports, we realized that by saving the last created SAS® dataset before each report, and converting these datasets to a standardized cell-based format, we are able to automate identifying the following discrepancies in the reports:

- Reports with undefined titles
- Missing footnote references
- Duplicate records in reports
- Report creation dates
- Empty reports
- SAS log file findings
- AE reports for discrepancies
- Hardcoded formats
- Reported Big N with each population
- And more…

We have learned that a key point in converting the last created SAS datasets to cell-based datasets is to identify fields in the reports that are values and fields that are properties of the values. Let's look at the following report (figure 1):

Table 1.1 / 1: Study sample sizes in extension by country and site (subjects enrolled in extension)

Country	Investigator Name	Date of the earliest consent	Date of the last visit	Number of subjects enrolled in extension (a)	Dosing Group in Extension	Number of subjects valid for safety	Number of subjects valid for ITT
Total		16MAY2012	10APR2019	36	Total	40	40
					Twice a week	4	4
					Every 5 days	12	12
					Every 7 days	8	8
					Variable frequency	16	16
AUSTRIA	Total	10OCT2012	20FEB2019	2	Total	2	2
					Variable frequency	2	2
	UNIV. PROF. DR. CHRISTOPHER	10OCT2012	20FEB2019	2	Total	2	2
BELGIUM	Total	24OCT2012		2	Total	2	2
					Twice a week	1	1
....	.....	....	....	..	.....	..	..

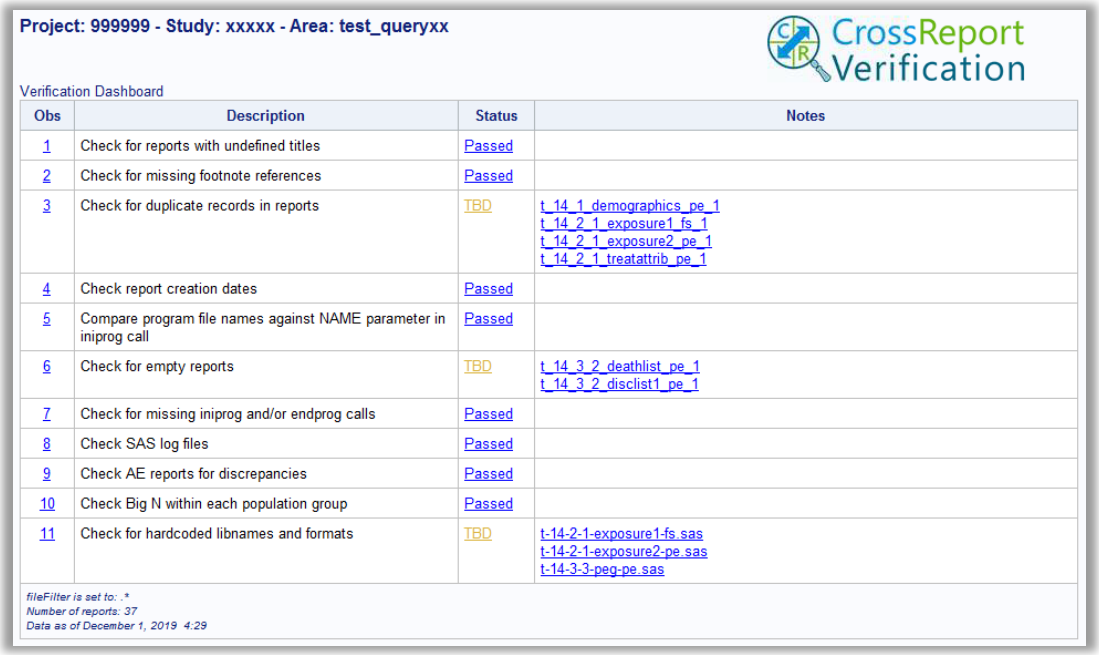
(a) Number of subjects enrolled is the number of subjects who signed informed consent for Part A extension.

Report Name: t-14-1-samplesizes-pe.sas 25NOV2019 22:57

Figure 1

Selected cell value "12", highlighted in the green box, has all the properties that are selected in the red boxes. Differentiating between a cell value and cell properties can be accomplished easily during the report creation by querying various SAS parameters such as Order, By, Title, and Footnote statements. We have learned that gathering this information by scanning the final SAS created output is cumbersome.

When we run checks against a study which has the supported cell-based dataset, an HTML page with hyperlinks to various programs, reports, and the findings is created. This dashboard (figure 2) provides a Table of Contents functionality for the entire report.



Project: 999999 - Study: xxxxx - Area: test_queryxx

CrossReport Verification

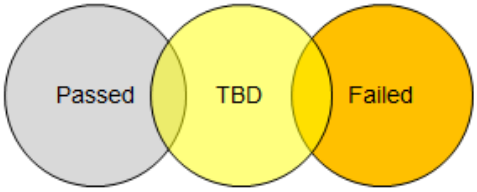
Verification Dashboard

Obs	Description	Status	Notes
1	Check for reports with undefined titles	Passed	
2	Check for missing footnote references	Passed	
3	Check for duplicate records in reports	TBD	t_14_1_demographics_pe_1 t_14_2_1_exposure1_fs_1 t_14_2_1_exposure2_pe_1 t_14_2_1_treatattrib_pe_1
4	Check report creation dates	Passed	
5	Compare program file names against NAME parameter in iniprog call	Passed	
6	Check for empty reports	TBD	t_14_3_2_deathlist_pe_1 t_14_3_2_disclist1_pe_1
7	Check for missing iniprog and/or endprog calls	Passed	
8	Check SAS log files	Passed	
9	Check AE reports for discrepancies	Passed	
10	Check Big N within each population group	Passed	
11	Check for hardcoded libnames and formats	TBD	t-14-2-1-exposure1-fs.sas t-14-2-1-exposure2-pe.sas t-14-3-3-peg-pe.sas

*fileFilter is set to: .**
Number of reports: 37
Data as of December 1, 2019 4:29

Figure 2

CHECK STATUS



Valid values for the Status fields are: Passed, Failed and TBD (To-Be-Determined).
For some checks we know whether the values are correct or not. An example would be checking for missing titles. Are the titles there? Yes or No.

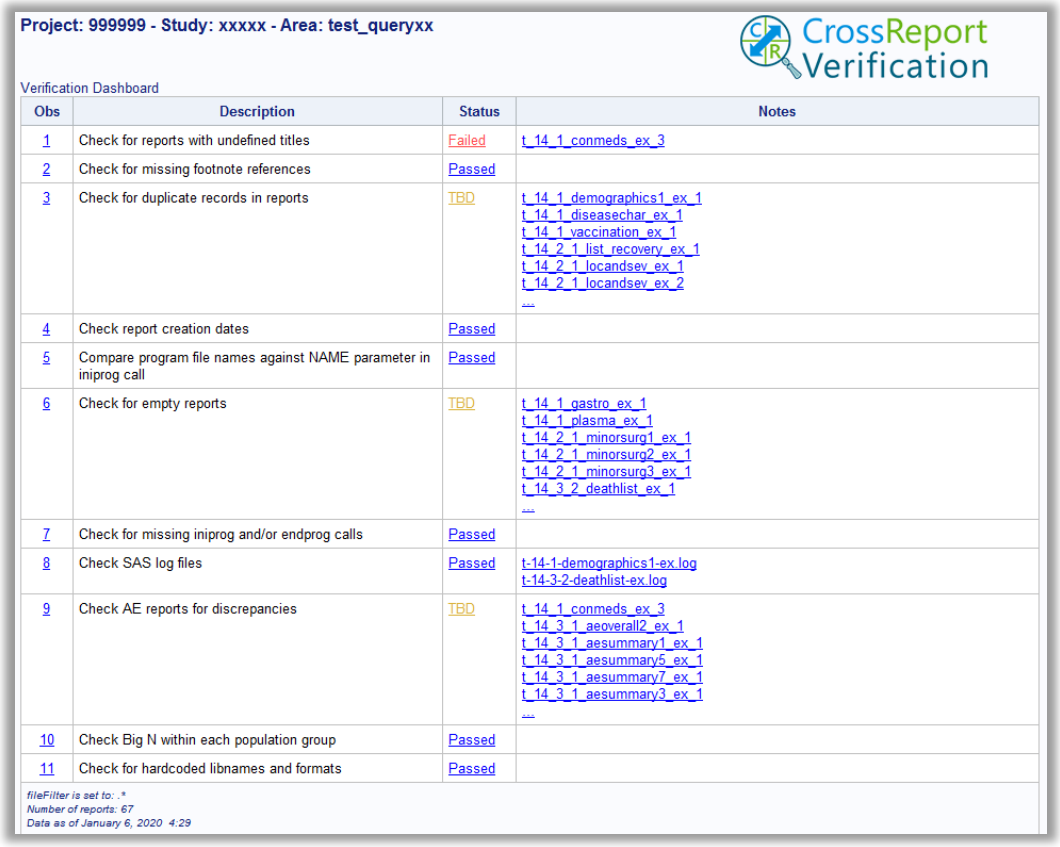
In TBD, the program cannot figure whether something is correct or not, so these findings need to be checked manually. An example would be “finding duplicate records.”.

CHECK FOR REPORTS WITH UNDEFINED TITLES

Once we create a standardized cell-based dataset for a set of Listings and Tables, identifying a missing title is a simple SAS code:

```
Proc Sort DATA=<cell_based dataset> OUT= result NODUPKEYS;
Where MISSING(Title1);
By Report_name;
Run;
```

Figure 3 is a sample dashboard for a selected study. Clicking on the Status field takes you to a summary report (figure 4) for the selected check. Clicking on the Obs field takes you to a detail report (figure 5) with identified discrepancies highlighted.



Project: 999999 - Study: xxxxx - Area: test_queryxx

CrossReport Verification

Verification Dashboard

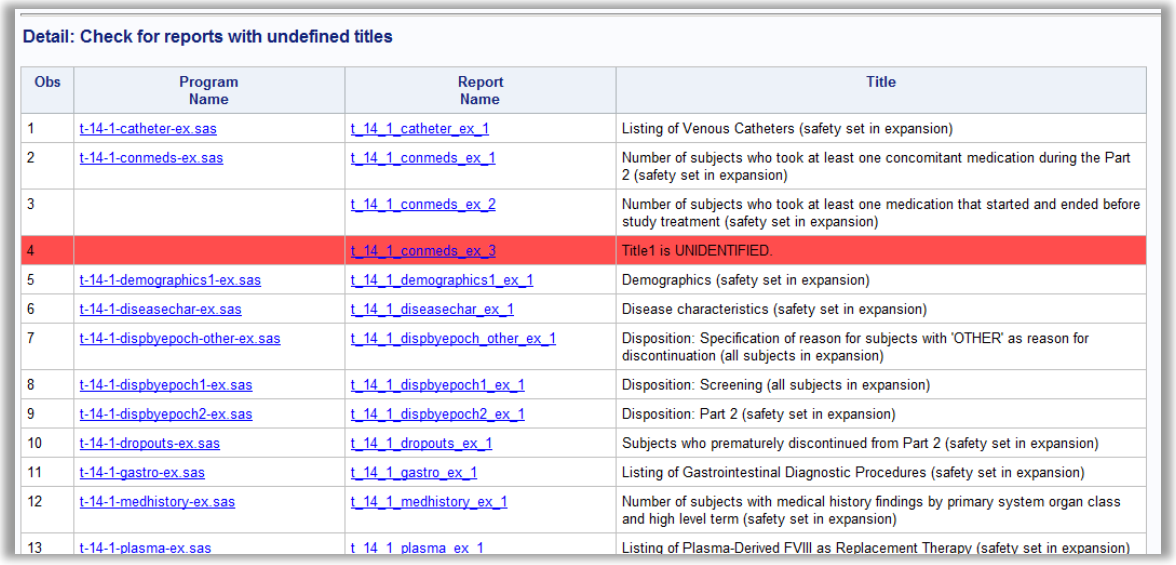
Obs	Description	Status	Notes
1	Check for reports with undefined titles	Failed	t_14_1_conmeds_ex_3
2	Check for missing footnote references	Passed	
3	Check for duplicate records in reports	TBD	t_14_1_demographics1_ex_1 t_14_1_diseasechar_ex_1 t_14_1_vaccination_ex_1 t_14_2_1_list_recovery_ex_1 t_14_2_1_locandsev_ex_1 t_14_2_1_locandsev_ex_2 ...
4	Check report creation dates	Passed	
5	Compare program file names against NAME parameter in iniprog call	Passed	
6	Check for empty reports	TBD	t_14_1_gastro_ex_1 t_14_1_plasma_ex_1 t_14_2_1_minorsurg1_ex_1 t_14_2_1_minorsurg2_ex_1 t_14_2_1_minorsurg3_ex_1 t_14_3_2_deathlist_ex_1 ...
7	Check for missing iniprog and/or endprog calls	Passed	
8	Check SAS log files	Passed	t-14-1-demographics1-ex.log t-14-3-2-deathlist-ex.log
9	Check AE reports for discrepancies	TBD	t_14_1_conmeds_ex_3 t_14_3_1_aeoverall2_ex_1 t_14_3_1_aesummary1_ex_1 t_14_3_1_aesummary5_ex_1 t_14_3_1_aesummary7_ex_1 t_14_3_1_aesummary3_ex_1 ...
10	Check Big N within each population group	Passed	
11	Check for hardcoded libnames and formats	Passed	

*fileFilter is set to: .**
Number of reports: 67
Data as of January 6, 2020 4:29

Figure 3

Note: Clicking on the program name displays its associated SAS Program and clicking on the report name displays its associated .rtf or .lst file.

Sample Detail check for reports with undefined titles:



Detail: Check for reports with undefined titles

Obs	Program Name	Report Name	Title
1	t-14-1-catheter-ex.sas	t_14_1_catheter_ex_1	Listing of Venous Catheters (safety set in expansion)
2	t-14-1-conmeds-ex.sas	t_14_1_conmeds_ex_1	Number of subjects who took at least one concomitant medication during the Part 2 (safety set in expansion)
3		t_14_1_conmeds_ex_2	Number of subjects who took at least one medication that started and ended before study treatment (safety set in expansion)
4		t_14_1_conmeds_ex_3	Title1 is UNIDENTIFIED.
5	t-14-1-demographics1-ex.sas	t_14_1_demographics1_ex_1	Demographics (safety set in expansion)
6	t-14-1-diseasechar-ex.sas	t_14_1_diseasechar_ex_1	Disease characteristics (safety set in expansion)
7	t-14-1-dispbyepoch-other-ex.sas	t_14_1_dispbyepoch_other_ex_1	Disposition: Specification of reason for subjects with 'OTHER' as reason for discontinuation (all subjects in expansion)
8	t-14-1-dispbyepoch1-ex.sas	t_14_1_dispbyepoch1_ex_1	Disposition: Screening (all subjects in expansion)
9	t-14-1-dispbyepoch2-ex.sas	t_14_1_dispbyepoch2_ex_1	Disposition: Part 2 (safety set in expansion)
10	t-14-1-dropouts-ex.sas	t_14_1_dropouts_ex_1	Subjects who prematurely discontinued from Part 2 (safety set in expansion)
11	t-14-1-gastro-ex.sas	t_14_1_gastro_ex_1	Listing of Gastrointestinal Diagnostic Procedures (safety set in expansion)
12	t-14-1-medhistory-ex.sas	t_14_1_medhistory_ex_1	Number of subjects with medical history findings by primary system organ class and high level term (safety set in expansion)
13	t-14-1-plasma-ex.sas	t_14_1_plasma_ex_1	Listing of Plasma-Derived FVIII as Replacement Therapy (safety set in expansion)

Figure 4

CHECK FOR MISSING FOOTNOTE REFERENCES

There are various ways a report can have discrepancies with footnote references. So far, we have identified the following scenarios:

1. Footnote without the corresponding reference
2. Value reference without a matching footnote
3. Column reference without a matching footnote
4. Row reference without a matching footnote
5. Row header reference without a matching footnote

Using the cell-based dataset, we are able to answer these questions programmatically.
Following is an example of a report where there is a footnote without any reference:

Table 14.1 / 1: Study sample sizes by country and site

Country	Study Site Name	Investigator Name	Date of first consent	Date of last visit in Part 2	Number of subjects enrolled in the study	Number of subjects valid for safety
Total			14OCT2015	15AUG2016	5	4
NEW ZEALAND	Total		04FEB2016	12JUL2016	4	3
	HAEMATOLOGY SERVICE	DR. Jon Dow	04FEB2016	03JUN2016	1	1
	WAIKATO HOSPITAL	DR. Jon Smith	14MAR2016	12JUL2016	3	2
UNITED STATES	Total		02MAR2016	24MAY2016	1	1
	PRIMARY CHILDREN'S HOSPITAL	DR. Jon Dow	02MAR2016	24MAY2016	1	1

(a) Number of subjects enrolled is the number of subjects who signed informed consent.

End of table

Figure 5

Figure 7 is a summary check for the above report (figure 6):

Summary: Check for missing footnote references

Obs	Program Name	Report Name	Column Reference Missing Footnote	Row Reference Missing Footnote	Row Header Reference Missing Footnote	Value Reference Missing Footnote	Footnote Without Any Reference	Referenced Footnote List
1	t-14-1-samplesizes-ex.sas	t_14_1_samplesizes_ex_1	No	No	No	No	Yes	(a) Number of subjects enrolled is the...

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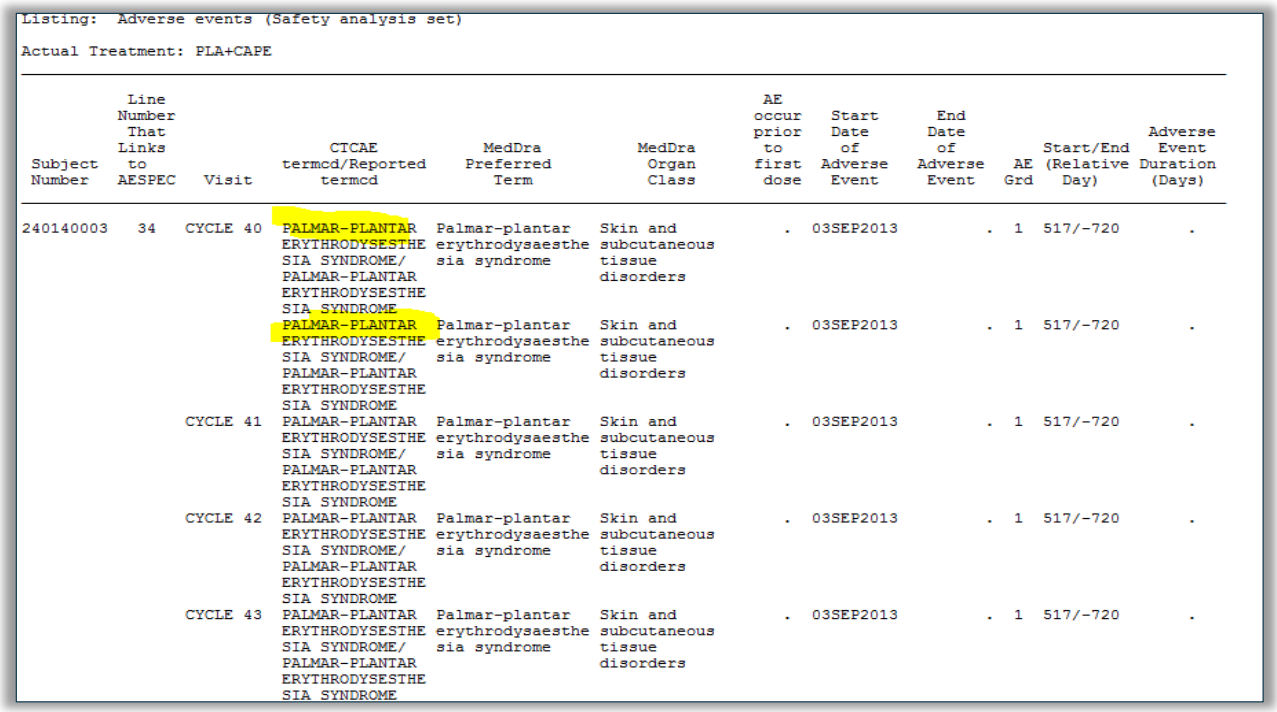
Figure 6

CHECK FOR DUPLICATE RECORDS IN REPORTS

This check identifies duplicate rows in the Table and Listing reports.
Following is the screenshot of a report with duplicate records (figure 8).



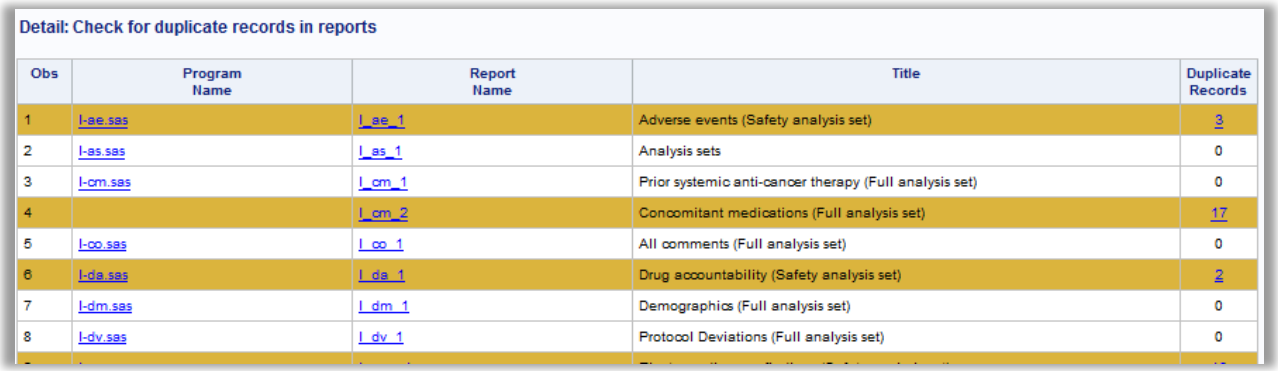
Listing: Adverse events (Safety analysis set)

Actual Treatment: PLA+CAPE

Subject Number	Line Number That Links to AESPEC	Visit	CTCAE termcd/Reported termcd	MedDra Preferred Term	MedDra Organ Class	AE occur prior to first dose	Start Date of Adverse Event	End Date of Adverse Event	AE Grd	Start/End (Relative Day)	Adverse Event Duration (Days)
240140003	34	CYCLE 40	PALMAR-PLANTAR ERYTHRODYSESTHESIA SYNDROME/ PALMAR-PLANTAR ERYTHRODYSESTHESIA SYNDROME	Palmar-plantar erythrodysaesthesia syndrome	Skin and subcutaneous tissue disorders	.	03SEP2013	.	1	517/-720	.
			PALMAR-PLANTAR ERYTHRODYSESTHESIA SYNDROME/ PALMAR-PLANTAR ERYTHRODYSESTHESIA SYNDROME	Palmar-plantar erythrodysaesthesia syndrome	Skin and subcutaneous tissue disorders	.	03SEP2013	.	1	517/-720	.
		CYCLE 41	PALMAR-PLANTAR ERYTHRODYSESTHESIA SYNDROME/ PALMAR-PLANTAR ERYTHRODYSESTHESIA SYNDROME	Palmar-plantar erythrodysaesthesia syndrome	Skin and subcutaneous tissue disorders	.	03SEP2013	.	1	517/-720	.
		CYCLE 42	PALMAR-PLANTAR ERYTHRODYSESTHESIA SYNDROME/ PALMAR-PLANTAR ERYTHRODYSESTHESIA SYNDROME	Palmar-plantar erythrodysaesthesia syndrome	Skin and subcutaneous tissue disorders	.	03SEP2013	.	1	517/-720	.
		CYCLE 43	PALMAR-PLANTAR ERYTHRODYSESTHESIA SYNDROME/ PALMAR-PLANTAR ERYTHRODYSESTHESIA SYNDROME	Palmar-plantar erythrodysaesthesia syndrome	Skin and subcutaneous tissue disorders	.	03SEP2013	.	1	517/-720	.

Figure 7

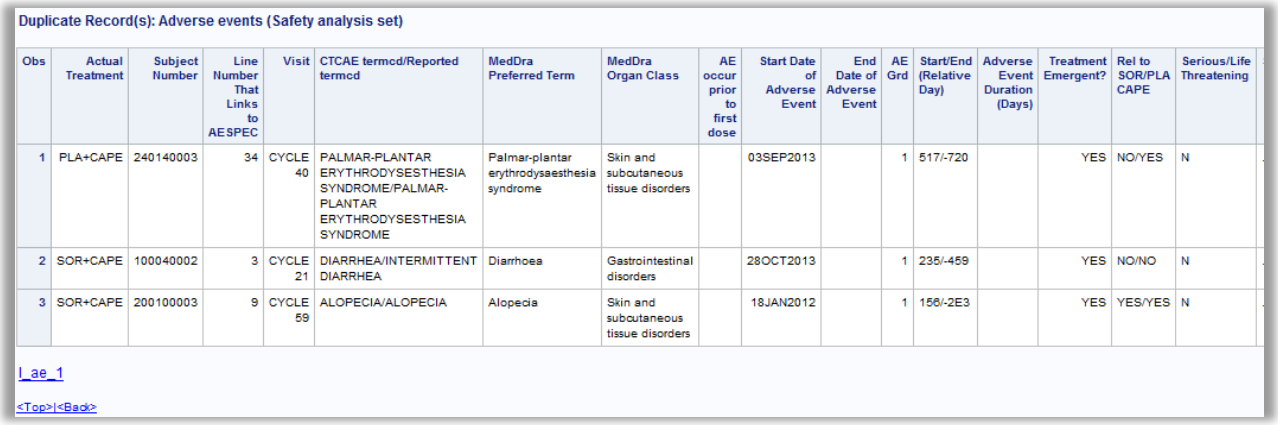
When running a check against a study that includes the above report (figure 8), this discrepancy will be identified.
First row in the summary report (figure 9) shows there are three duplicate AE records.
Clicking on the number "3" in the duplicate records column will display the three duplicate records (figure 10).



Detail: Check for duplicate records in reports

Obs	Program Name	Report Name	Title	Duplicate Records
1	l-ae.sas	l_ae_1	Adverse events (Safety analysis set)	3
2	l-as.sas	l_as_1	Analysis sets	0
3	l-cm.sas	l_cm_1	Prior systemic anti-cancer therapy (Full analysis set)	0
4		l_cm_2	Concomitant medications (Full analysis set)	17
5	l-co.sas	l_co_1	All comments (Full analysis set)	0
6	l-da.sas	l_da_1	Drug accountability (Safety analysis set)	2
7	l-dm.sas	l_dm_1	Demographics (Full analysis set)	0
8	l-dv.sas	l_dv_1	Protocol Deviations (Full analysis set)	0

Figure 8



Duplicate Record(s): Adverse events (Safety analysis set)

Obs	Actual Treatment	Subject Number	Line Number That Links to AESPEC	Visit	CTCAE termcd/Reported termcd	MedDra Preferred Term	MedDra Organ Class	AE occur prior to first dose	Start Date of Adverse Event	End Date of Adverse Event	AE Grd	Start/End (Relative Day)	Adverse Event Duration (Days)	Treatment Emergent?	Rel to SOR/PLACAPE	Serious/Life Threatening
1	PLA+CAPE	240140003	34	CYCLE 40	PALMAR-PLANTAR ERYTHRODYSESTHESIA SYNDROME/PALMAR-PLANTAR ERYTHRODYSESTHESIA SYNDROME	Palmar-plantar erythrodysaesthesia syndrome	Skin and subcutaneous tissue disorders		03SEP2013		1	517/-720		YES	NO/YES	N
2	SOR+CAPE	100040002	3	CYCLE 21	DIARRHEA/INTERMITTENT DIARRHEA	Diarrhoea	Gastrointestinal disorders		28OCT2013		1	235/-459		YES	NO/NO	N
3	SOR+CAPE	200100003	9	CYCLE 59	ALOPECIA/ALOPECIA	Alopecia	Skin and subcutaneous tissue disorders		18JAN2012		1	156/-2E3		YES	YES/YES	N

l_ae_1

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Figure 9

The above report (figure 10) indicates three separate duplicate records in the AE listing.
Clicking on the report name on the last line will display the actual report (figure 8).

CHECK REPORT CREATION DATES

Let's say you have a file that includes a number of SAS programs. All your programs work at first. But due to arrival of new data, for instance a new visit is added, one of the programs stops working. Now you are working with an outdated file in the middle of your TLF report. The object of this check is to help identify these outdated reports.
If the gap between report creation date and that of the most recent report is greater than a certain time window, the report is flagged.

CHECK FOR EMPTY REPORTS

All reports that contain no data are flagged.

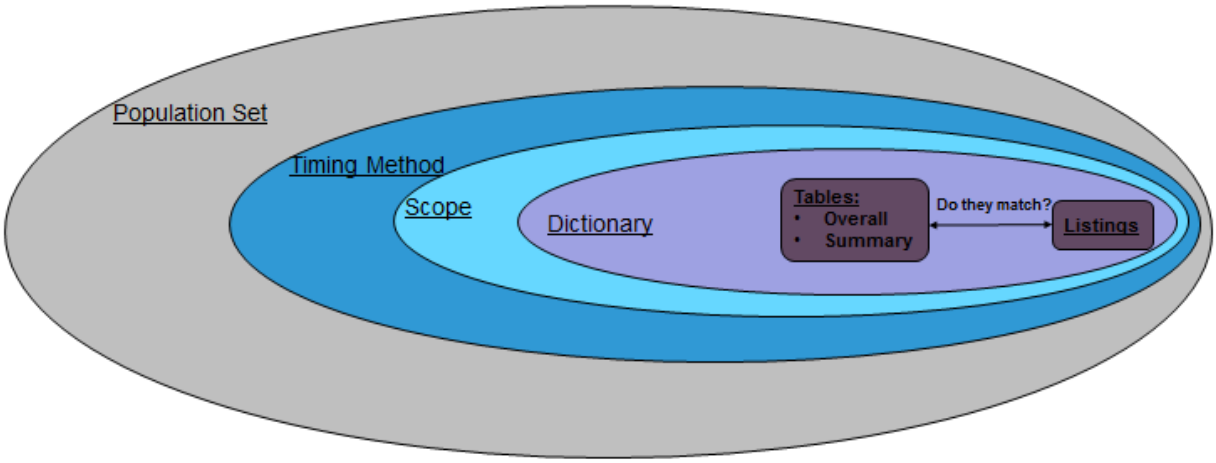
CHECK SAS LOG FILES

SAS log files are scanned for the presence of ERRORs, WARNINGs and critical NOTEs. Reports are flagged if any such findings are detected.

CHECK AE REPORTS FOR DESCREPANCIES

Numbers among AE Summary, Overall and Listing reports are checked for consistency.
We take AE reports based on their titles and group them to the following categories:
Population Set, Timing Method, Scope, Dictionary.
The numbers in the AE columns of the Table report and the number of lines in the Listing report must match. If not, the report is flagged.

For example, if we take all the study AE reports written for the intent-to-treat population set, and from that group select all the Treatment Emergent reports, and from that new subgroup of reports select all the SAE reports that used the same dictionary, the number of rows in the Listing and the total columns in the Table reports has to match. If not, the report is flagged.



AE reports are grouped to the following categories:
Population Set: safety analysis set, full analysis set, intent-to-treat, per-protocol,…
Timing Method: _all_, Treatment Emergent, Cutoff, After, Before, Between, Phase, Pre/Post treatment, …
Scope: Any AE, SAE, Severe, Related, SAE, Discontinuation, non-Serious
Dictionary: MedDRA, CTCAE, MedDRA/CTCAE (not specified defaults to MedDRA)

Figure 11 is an example of checking for AE discrepancies. Two reports are flagged because the total column in the table does not match the number of lines with the associated listing report.

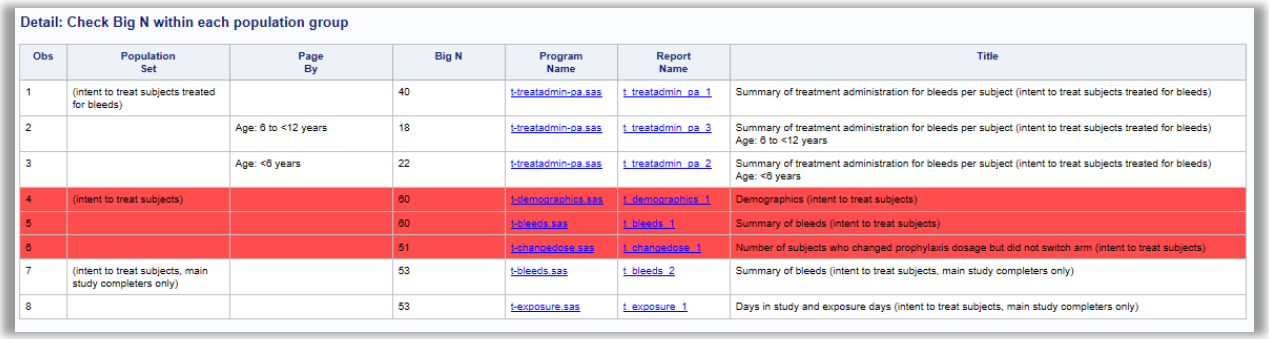
Detail: Check AE reports for discrepancies

Obs	Population Set	Timing Method	Scope	Dictionary	Output Type	Total	Program Name	Report Name	Title
1	(intent-to-treat)	Treatment Emergent	AnyAE	MedDRA	Table	37	t-aeoverall.sas	t_aeoverall-1	Overall summary of number of subjects with adverse events in extension (intent-to-treat)
2						37	t-aesummary.sas	t_aesummary-1	Number of subjects with adverse events by primary system organ class and preferred term in extension (intent-to-treat)
3			Related	MedDRA	Table	3	t-aesummary2.sas	t_aesummary2-1	Number of subjects with drug-related adverse events by primary system organ class, preferred term in extension (intent-to-treat)
4			SAE	MedDRA	Listing	16	t-saelist.sas	t_saelist-1	Listing of serious adverse events in extension (intent-to-treat)
5					Table	15	t-aesummary3.sas	t_aesummary3-1	Number of subjects with serious adverse events by primary system organ class, preferred term in extension (intent-to-treat)
6			Terms	MedDRA	Listing	207	t-aeterms.sas	t_aeterms-1	Adverse event terms and associated reported terms in extension coded by MedDRA version 22.0 (intent-to-treat)

Figure 10

CHECK FOR BIG N WITH EACH POPULATION

Check reports for discrepancies in reporting Big N for various populations. Reports in which Big N does not match within a population are flagged.
Sample HTML detail report (figure 12):



Detail: Check Big N within each population group

Obs	Population Set	Page By	Big N	Program Name	Report Name	Title
1	(intent to treat subjects treated for bleeds)		40	t-treatadmin-pa.sas	t_treatadmin_pa_1	Summary of treatment administration for bleeds per subject (intent to treat subjects treated for bleeds)
2		Age: 6 to <12 years	18	t-treatadmin-pa.sas	t_treatadmin_pa_3	Summary of treatment administration for bleeds per subject (intent to treat subjects treated for bleeds) Age: 6 to <12 years
3		Age: <6 years	22	t-treatadmin-pa.sas	t_treatadmin_pa_2	Summary of treatment administration for bleeds per subject (intent to treat subjects treated for bleeds) Age: <6 years
4	(intent to treat subjects)		60	t-demographics.sas	t_demographics_1	Demographics (intent to treat subjects)
5			60	t-bleeds.sas	t_bleeds_1	Summary of bleeds (intent to treat subjects)
6			51	t-changedose.sas	t_changedose_1	Number of subjects who changed prophylaxis dosage but did not switch arm (intent to treat subjects)
7	(intent to treat subjects, main study completers only)		53	t-bleeds.sas	t_bleeds_2	Summary of bleeds (intent to treat subjects, main study completers only)
8			53	t-exposure.sas	t_exposure_1	Days in study and exposure days (intent to treat subjects, main study completers only)

Figure 11

CHECK FOR HARDCODED FORMATS

Check for hardcoded libnames and formats. SAS programs are scanned for the presence of LIBNAME and PROC FORMAT statements.

Figure 13 is a sample report of a check for hardcoded report.

Detail: Check for hardcoded libnames and formats

Obs	Program Name	Hardcoded Libnames	Hardcoded Formats
1	t_effic_dosefreq.sas	✔	✔
2	t_demog_samplesize.sas	LIBNAME temp "&tempdir";	✔
3	t_effic_bleeds.sas	✔	✔
4	t_effic_dosefreq.sas	✔	PROC FORMAT; VALUE _dosfrq 4 = 'On-Demand' 17 = 'Twice a week' 27 = 'Every 5 days' 28 = 'Every 7 days'; RUN;
5	t_effic_exposure.sas	✔	✔

Figure 12

CONCLUSION

In this presentation we presented the use of SAS macros to create a cell-based data set for each reporting event and implement various cross-report verification checks.

A limitation of our method is that verification checks are made on the SAS data sets used to create TLFs, rather than on the text contained in the PDF output of the TLFs themselves. Therefore, this solution is not a replacement for visual verification. You should always quality check your deliverables before sending it to your study teams.

Overall, we find that developing an automated cross-report verification system is helpful in completing the review process necessary to produce large and complex Clinical Study Reports with high accuracy and integrity.

Of note we have identified that the derived cell-based datasets enable us to pool reports across reporting events and providing information difficult to compile previously. Using these datasets, we are able to:

- Reproduce reports in various formats such as JSON, XML, RDF, and Excel
- Recreate listing reports for a subset of data
- Convert Table and Listing reports to organizational digital assets

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