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The Ultimate Integration Challenge

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ABSTRACT

In 2008, Covance was awarded the ultimate challenge to develop a CDISC compliant data warehouse of over thirty multiple Phase I through to Phase III studies.

The paper will cover how the Programmers and Statisticians leveraged their experiences in dealing with large and complex data integration where the data were received through multiple providers with different structures and variable attributes. The aim was to engineer the best enhancement solutions to achieve data uniformity and harmonisation across studies that were fully compliant with the regulatory standards for submissions.

INTRODUCTION

Covance was contracted to perform a step-wise integration of data from over thirty studies across Phases I – III into a CDSIC compliant data warehouse for an Integrated Summary of Safety (ISS) and Integrated Summary of Efficacy (ISE) for the New Drug Application (NDA) and the European Medicines Evaluation Agency (EMEA) submissions in 2009. At the time of the request, Covance was involved with 1 of the 3 pivotal studies with the remaining studies coming from multiple providers. Parallel teams at Covance worked concurrently on the ISS/ISE and the pivotal studies to ensure timely delivery of final integrated tables and reports.

Over thirty multiple Phase I through to Phase III studies contributed to the safety warehouse. The data warehouse comprised of 12% Phase III, 15% Phase II and 73% Phase I studies. There were 162 SDTMs and 226 ADaMs datasets created, providing a total of 6,747 patients in the integrated safety database. Of which, 41% of the patients were contributed from the Phase III, 40% from the Phase II and 19% contributed from the Phase I. Two of the Phase III studies contributed more than 12 months long-term data. All pivotal studies were double-blind, placebo-controlled studies and with one of them being an open-label controlled extension study. Seventy percents of the Phase I data were in clinical pharmacology PK and PD studies in normal healthy volunteers and the remaining were in special population groups.

For the ISS, the safety population was categorised into 4 main study groups, which were further divided into sub-groups. Different studies contributed to different treatment groups within each study group. The first and most important study group consisted of all data from the pivotal studies. The second study group consisted of placebo controlled groups from healthy volunteers. The third study group consisted of PK/PD data from single dose and multiple dose studies. The fourth study group consisted of data from studies based on special concerns and special populations.

For this paper, we focused our attention mainly on the integration data challenges associated with the safety analyses for the ISS which was far more complex than the ISE in comparison.

INTEGRATION DATA CHALLENGES

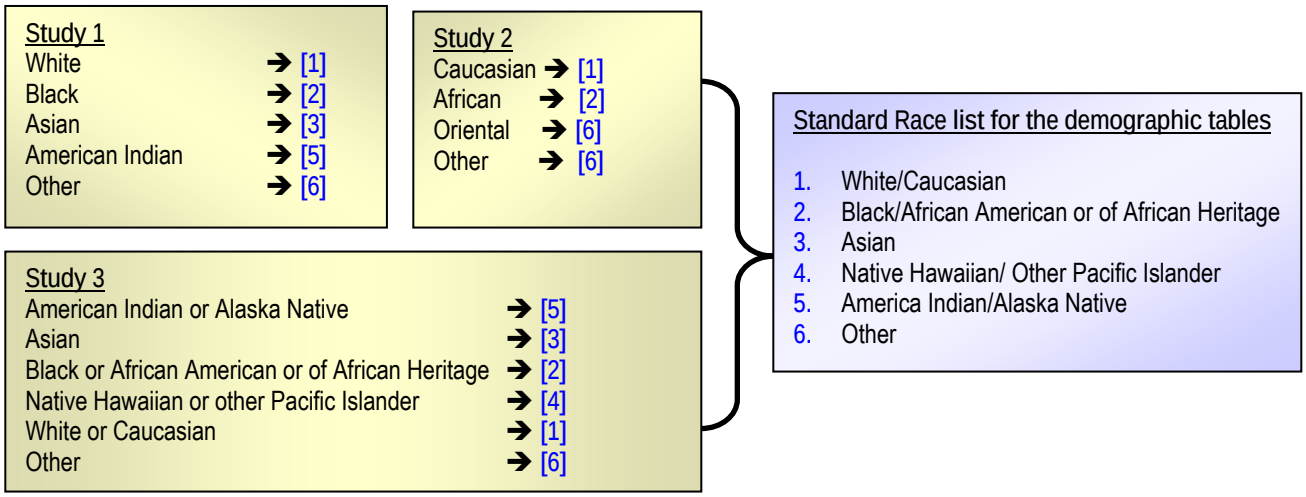
Consistency of approach and harmonisation of variables from different database structures are critical factors to achieve a standardised CDISC compliant warehouse. Data from multiple providers present some real challenges as naming conventions, variable attributes, programming algorithms and assumptions can vary enormously from one provider to another. Many of the studies that were integrated into the data warehouse were in non-CDISC compliant format.

This paper illustrates some of the data integration challenges that Covance faced and describes the approach taken to aim for best enhancement solutions to build the CDISC compliant data warehouse. We will provide some examples of problems encountered in merging data recorded and coded in different ways, and also of challenges faced when pooling data into different safety populations and treatment groups.

DATA VARIATION AND HARMONIZATION

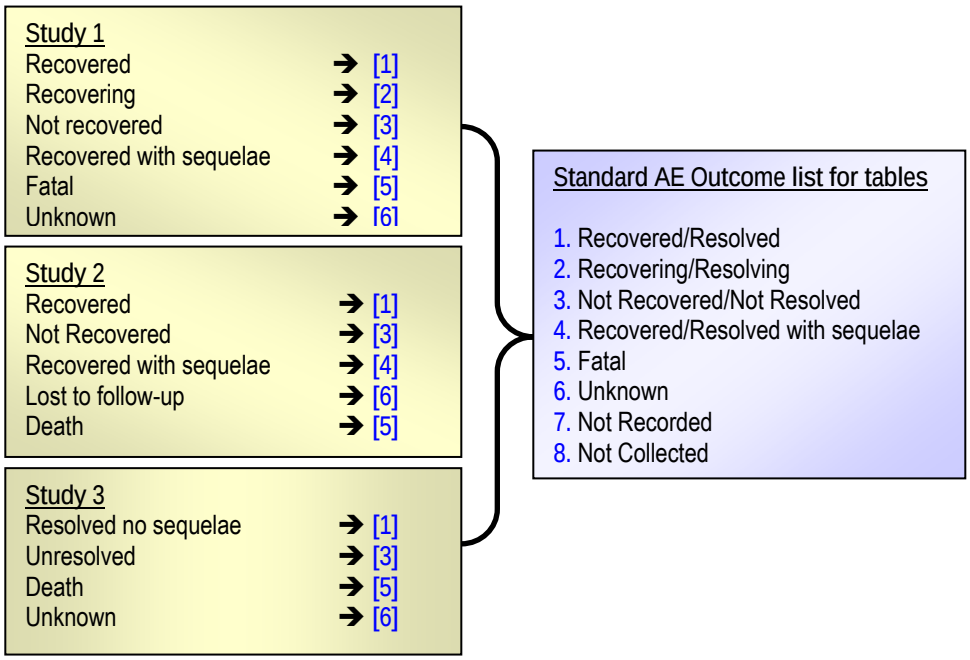
1. RACE

Given the number of studies involved in the integration, it was expected that the Race information would vary from study to study. In studies where SDTMs were created, we adopted a two step approach; the first step was to map the Race variable from the raw dataset to SDTM (DM domain) and the second step was to derive the Race values in ADaM datasets from the SDTM as per the standard Race list required in the demographic table. In studies where ADaM datasets were created directly from the raw datasets, the approach was to derive the Race values in ADaM datasets from the raw data. The following diagrams provide the mapping for Race. The number in brackets indicates the values from the individual study which were used to compile the Global Race list used for the safety analyses.



2. ADVERSE EVENT OUTCOME

The following illustrates the variations in the recording of the AE outcome across studies. The values under individual studies were mapped to a standard list approved by the Sponsor



3. ADVERSE EVENT SEVERITY

AE severity information was consistent across all studies except one. In one of the Phase III studies, two severities; initial severity and maximum severity were recorded on the Case Report Form (CRF) for each incidence of adverse event. The initial severity was related to the start of the adverse event. If there were fluctuations in AE severity until the resolution of the AE then the maximum among all severities was recorded along with the date it occurred. If there was no change in severity then the initial severity would be the same as the maximum severity. For the integrated database, both severities and the date of severity changes were retained but the maximum severity was reported in the summary outputs. Any missing severity was imputed to the worst case as 'Severe'.

4. ADVERSE EVENT RELATIONSHIP

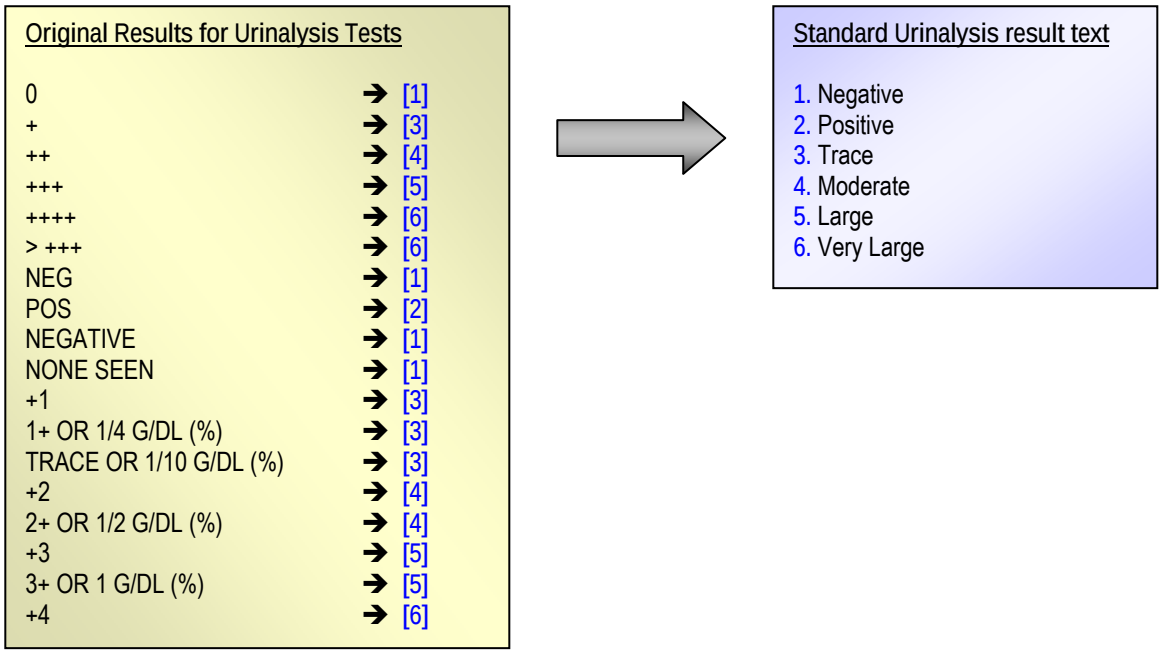
Whether an AE was related to the Investigational Medicinal Product (IMP) was not recorded for all studies. In such cases, no imputation rule was applied and the relationship for these events was assigned as 'Not Collected'.

5. DISPOSITION vs. DISCONTINUATION DUE TO AE

The discontinuation from study due to AE was captured in the Study Completion/End of Study (disposition) CRF page as well as in the adverse event CRF page where an event could lead to the patient being discontinued from the study. For Phase I and II studies, multiple reasons for discontinuation were recorded in the study completion CRF page and a primary reason for discontinuation was assigned through medical review of the reasons. Discrepancies were observed between the total number of patients with any AE leading to discontinuation and the total number of patients whose primary reason was discontinuation due to AE in the Disposition summary. Such discrepancies were documented by study treatment groups and patient listing and included in the data definition table of the integration database specifications document.

6. URINALYSIS TEST RESULTS

The diagram below illustrates the variations in recording the Urinalysis Laboratory test results on the CRF page. In the case of symbols these had to correctly decode to the corresponding text value.

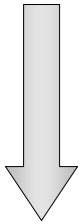


7. VITAL SIGNS: RECORDING POSITION AND TIME INTERVAL

For some of the studies, the assessment numbers corresponding to each visit denoted the Vital Signs recording positions (such as Supine, Standing, etc) and time interval between multiple tests. The difficulty here was that there were no formats available to decode the assessment numbers in order to identify the position and the time interval between two readings of the same BP test. The formats had to be created using the study flow chart which provided the relevant information. Moreover, one could not expect the assessment number and its corresponding description to be the same across the studies. The example below illustrates how information from the flow chart was used to create various variables in the dataset.

FLOW CHART INFORMATION

	Day 1	Day 2	Day 3	Week 1
Visit	2	2.5	3	4
Before dose	-1	71	71	71
1h after	72	72	72	
2h after	73	73	73	
2-3h after				75
3h after	74	74	74	
4h after	76	76	76	
5h after	77	77	77	
6h after	78	78	78	



Assmt No.	Description
-10	Given to all measurements at screening visit (visit 1)
-1	Given to all measurements taken before first IP dose at visit 2
71	Given to extra safety monitoring measurements taken before dose at visits 2.5, 3, 4
72	Given to extra safety monitoring measurements taken 1 hour after dose at visits 2, 2.5, 3
73	Given to extra safety monitoring measurements taken 2 hour after dose at visits 2, 2.5, 3
74	Given to extra safety monitoring measurements taken 3 hour after dose at visits 2, 2.5, 3
75	Given to extra safety monitoring measurements taken 2-3 hour after dose at visit 4
76	Given to extra safety monitoring measurements taken 4 hour after dose at visits 2, 2.5, 3
77	Given to extra safety monitoring measurements taken 5 hour after dose at visits 2, 2.5, 3
78	Given to extra safety monitoring measurements taken 6 hour after dose at visits 2, 2.5, 3
xx	For all measurements of supine BP and Pulse after 15 mins of resting
xx.10	For all measurements of standing BP and Pulse after 2 mins of standing
xx.20	For all measurements of standing BP and Pulse after 5 mins of standing
xx = Assessment Number	

VARIABLES IN THE DATASET

VSPOS	VISIT	VSTPT1	VSTPT2
Supine	2	Before intake of IP	After 15 mins of Resting
Standing	2.5	1 hour after administration of IP	After 2 mins of Standing
	3	2 hours after administration of IP	After 5 mins of Standing
	4	3 hours after administration of IP	
		4 hours after administration of IP	
		5 hours after administration of IP	
		6 hours after administration of IP	

8. LABORATORY DATA

The harmonisation of lab data from all studies, across all phases was the first challenge we faced. For Phase II studies in particular, we had inconsistencies and variations in the laboratory data. Some of the main ones were: 1) the variation within the laboratory test code values, 2) not all laboratory test results were recorded in standard units and, 3) Potentially Clinically Significant (PCS) criteria differed from both original and standardised units, each presenting a challenge of its own.

8.1 LABORATORY TEST CODES

At the study level, the original lab test codes were numeric and the corresponding character values were determined using the source lab test formats. To complicate it further, the test code values had to be standardised at the individual study levels, as they differed from study to study e.g. Blood Urea Nitrogen was reported as UN, Urea and XUN in three different studies. In order to standardise, a comprehensive list of the diverse lab test codes was created and each value was mapped to a standardised list of test codes to eliminate variation and to ensure consistency in reporting.

	LAB CATEGOR	RAW LAB TEST SHORT NAME	RAW LAB TEST NAME	NEW LAB SHORT TEST NAM	NEW LAB TEST NAME
2	CHEMISTRY	XGP	ALAT (SGPT)	ALT	ALANINE AMINOTRANSFERASE
3	CHEMISTRY	ALAT		ALT	ALANINE AMINOTRANSFERASE
4	CHEMISTRY	XAL	ALBUMIN	ALB	ALBUMIN
5	CHEMISTRY	Alb		ALB	ALBUMIN
6	CHEMISTRY	XLK	ALKALINE PHOSPHATASE	ALP	ALKALINE PHOSPHATASE
7	CHEMISTRY	ALP		ALP	ALKALINE PHOSPHATASE
8	CHEMISTRY	XGO	ASAT (SGOT)	AST	ASPARTATE AMINOTRANSFERASE
9	CHEMISTRY	ASAT		AST	ASPARTATE AMINOTRANSFERASE
10	CHEMISTRY	StBic		CO2	BICARBONATE
11	CHEMISTRY	XBT	BILIRUBIN, TOTAL	BILI	BILIRUBIN, TOTAL
12	CHEMISTRY	Bili, tot		BILI	BILIRUBIN, TOTAL
13	CHEMISTRY	UN		BUN	BLOOD UREA NITROGEN
14	CHEMISTRY	Urea		BUN	BLOOD UREA NITROGEN
15	CHEMISTRY	XUN	UREA NITROGEN	BUN	BLOOD UREA NITROGEN
16	CHEMISTRY	XAB	CALCIUM	CA	CALCIUM
17	CHEMISTRY	Ca		CA	CALCIUM
18	CHEMISTRY	Cl		CL	CHLORIDE
19	CHEMISTRY	XCH	CHOLESTEROL, TOTAL	CHOL	CHOLESTEROL, TOTAL

8.2 LABORATORY TEST UNITS

Whilst producing the lab test codes list, we encountered the next hurdle – within each laboratory test that was done, the data were not consistently collected in the same units. This meant that conversions throughout the entire database would have to be done to ensure that all the different laboratory tests were presented in the same units. It was an enormous task to identify and collect the different units each lab test was presented in and to display the conversion logic from each unit to the standardised unit. It took the team over a month to complete the LB SDTM dataset.

8.3 POTENTIALLY CLINICALLY SIGNIFICANT CRITERIA

The definition for PCS Criteria was not part of the individual study Statistical Analysis Plan (SAP) but this was included in the SAP for the integration for ISS. When we compared the PCS units against the now standardised laboratory results, we soon realised that the PCS results in some cases were reported in different units than the original or even the standard units the laboratory results had now been converted to.

First we identified all lab tests where such differences existed and made the appropriate programmatic updates. Then a laboratory preface table was produced to display the information. Table 1 is an example of the laboratory preface illustrating the difference in units.

TABLE 1

Laboratory Evaluations Preface
Listing of Normal Ranges and Potentially Clinically Significant Criteria for Laboratory Tests

Laboratory Group Laboratory Test	Study	Unit		Gender	Age Range (years)	Limits of Normal Range		Predefined Potentially Clinically Significant (PCS) Criteria	
		NR	PCS Criterion			Lower Limit	Upper Limit	PCS Low Criterion	PCS High Criterion
Eosinophils *	ABC123	%	%	Male	<65	0	6.8		>=10
					>=65	0	6.8		>=10
				Female	<65	0	6.8		>=10
					>=65	0	6.8		>=10
	ABC111	10^9/L	%	Male	<65	0	0.45		>=10
					>=65	0	0.45		>=10
				Female	<65	0	0.45		>=10
					>=65	0	0.45		>=10
Basophils *	ABC123	%	%	Male	<65	0	2		>=5
					>=65	0	2		>=5
				Female	<65	0	2		>=5
					>=65	0	2		>=5
	ABC111	10^9/L	%	Male	<65	0	0.2		>=5
					>=65	0	0.2		>=5
				Female	<65	0	0.2		>=5
					>=65	0	0.2		>=5

Program: tlabpref.sas Output: tlabpref.lst
Notes: * PCS criteria for WBC differentials are derived by calculating the absolute value as a percentage of the whole WBC count.
NR = Normal Range, NA = Not Applicable.

DERIVATIONS

9. STUDY GROUP DERIVATIONS

The challenge in the Study Group derivation was the complexity of classifying the various treatments groups and sub analyses required for the ISS.

For the safety analyses, completed studies were organized into groups of commonality based on the population studied (patients or healthy subjects), study design, and availability of data (during a specific period of interest) for incorporating into an electronic ISS database. There were four study groups (Groups 1 to 4) defined for completed studies.

Each group had multiple sub-groups defined based on certain common aspects namely study design, period of interest, treatment exposure and patient population. For example within Group 1:

- Study group SG-10 consisted of completed Phase II/III double-blind, placebo-controlled studies and one open-label extension
- Study group SG-11 consisted of completed Phase II/III double-blind, placebo-controlled studies looking at data for a specfic period (e.g up to first 13 weeks). Within this sub-group, further sub analyses were performed based on various data points of interest namely, the target location, demographic characteristics, study exposure or phase, duration of the study period (e.g 6 weeks, 13 weeks, 26 weeks)
- Study group SG-12 consisted of Phase III open label studies
- Study group SG-13 consisted of patients from two Phase III double-blind, placebo-controlled studies and one open label extension study, who had been exposed to >= 26 weeks of Active or Active Control treatment
- Study group SG-14 consisted of patients from two Phase III double-blind, placebo-controlled studies and one open label extension study, who had been exposed to >= 52 weeks of Active or Active Control treatment

The table below summarizes the number of studies from each study phase associated with each of the main groups and their corresponding sub-groups

		Study Phase		
Group	Sub Group	I	II	III
1	SG-10		3	4
1	SG-11		3	3
1	SG-12			2
1	SG-13			3
1	SG-14			3
2	SG-20		2	
3	SG-31	9		
3	SG-32	8		
4	SG-41	3		
4	SG-42	5		

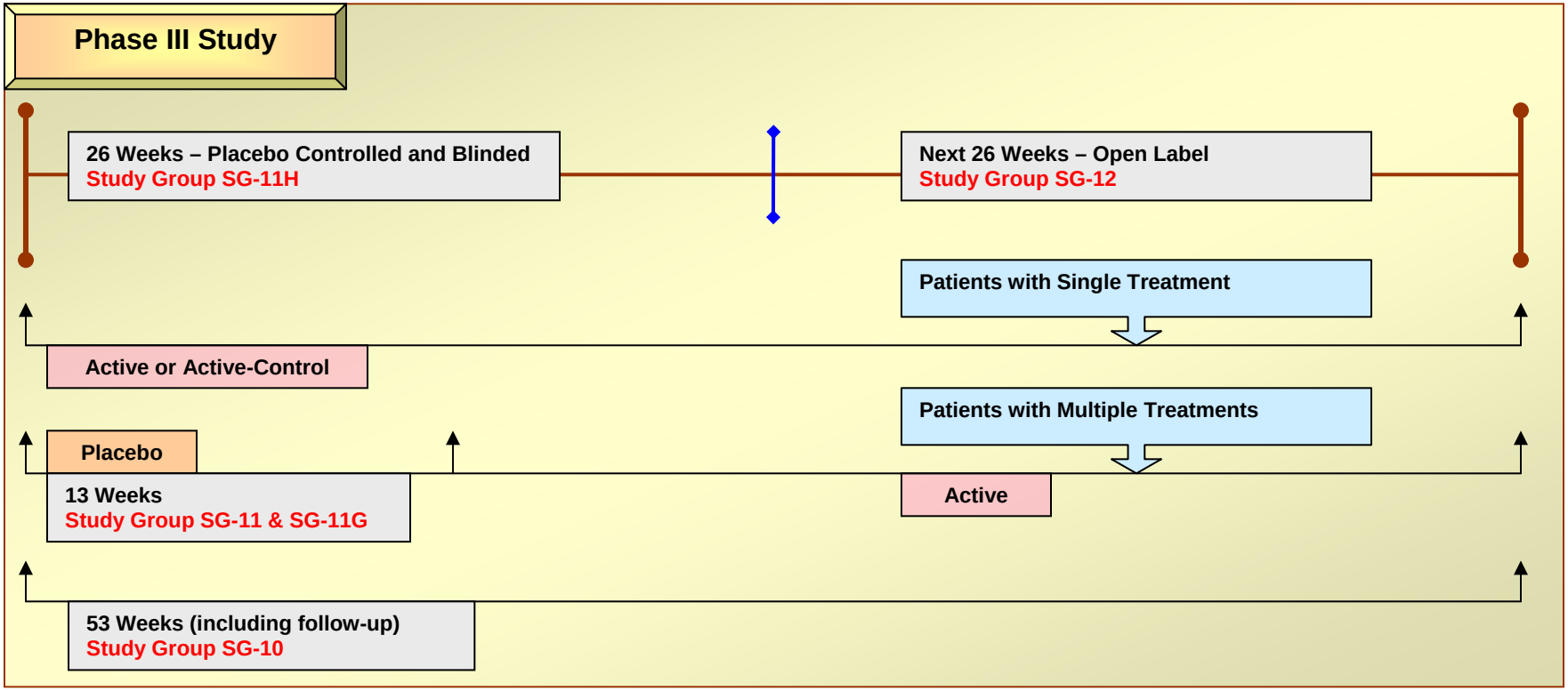
It should be noted that for the purpose of data displays, each study group had a defined set of treatment groups in which the data were summarized. Table 2 shows examples of the treatment groups which were included in the displays for each study group.

Table 2

		Treatment Groups for Displays							
Sub-Group	Description	All ACT	Placebo	Act-Con	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5
SG-10	Completed Phase 2/3 Clinical Studies	√	√	√	√		√		
SG-11	All Placebo-Controlled Studies (all data up to 13 Weeks)	√	√	√		√	√		
SG-11A	All Placebo-Controlled Studies (all data up to 13 Weeks) by Age, Gender,	√	√	√		√	√		
SG-11B	All Placebo-Controlled Studies (all data up to 13 Weeks) by Specific Body Site	√	√	√		√	√		
	… etc for other characteristics of interest								
SG-12	Open-Label (Extension)	√	√	√	√		√		√
SG-13	Only patients with ≥ 26 weeks of treatment exposure	√	√	√		√			
SG-14	Only patients with ≥ 52 weeks of treatment exposure	√	√	√	√				
SG-20	Placebo-Controlled Studies in Healthy Subjects	√	√	√			√	√	
SG-31	Single-Dose Studies in Healthy Subjects	√	√	√		√	√	√	
SG-32	Multiple-Dose Studies in Healthy Subjects	√	√	√	√		√		√
SG-41	Blood Pressure Monitoring Studies	√	√	√		√		√	√
SG-42	Special Populations	√	√	√	√				√
ACT : All doses of Active Treatment Act-Con : Active Control Treatment Note : Doses 1 – 5 were Active Treatment									

Figure 1 below illustrates how a study could be included in several sub-groups based on its design and the treatments involved. A good example was one of the Phase III studies where a group of patients was exposed to single treatment whereas another group was exposed to multiple treatments. The study had two parts; the first part of the study was double-blind, placebo-controlled and the second part was open label.

Figure 1



10. TREATMENT EXPOSURE:
Treatment Exposure was defined as the period when a patient was exposed to one or more IMPs for a fixed duration within a study. For most of the studies it was relatively straightforward except in the case of two pivotal Phase III studies, one of them being an open-label controlled extension to the parent double-blind, placebo controlled study

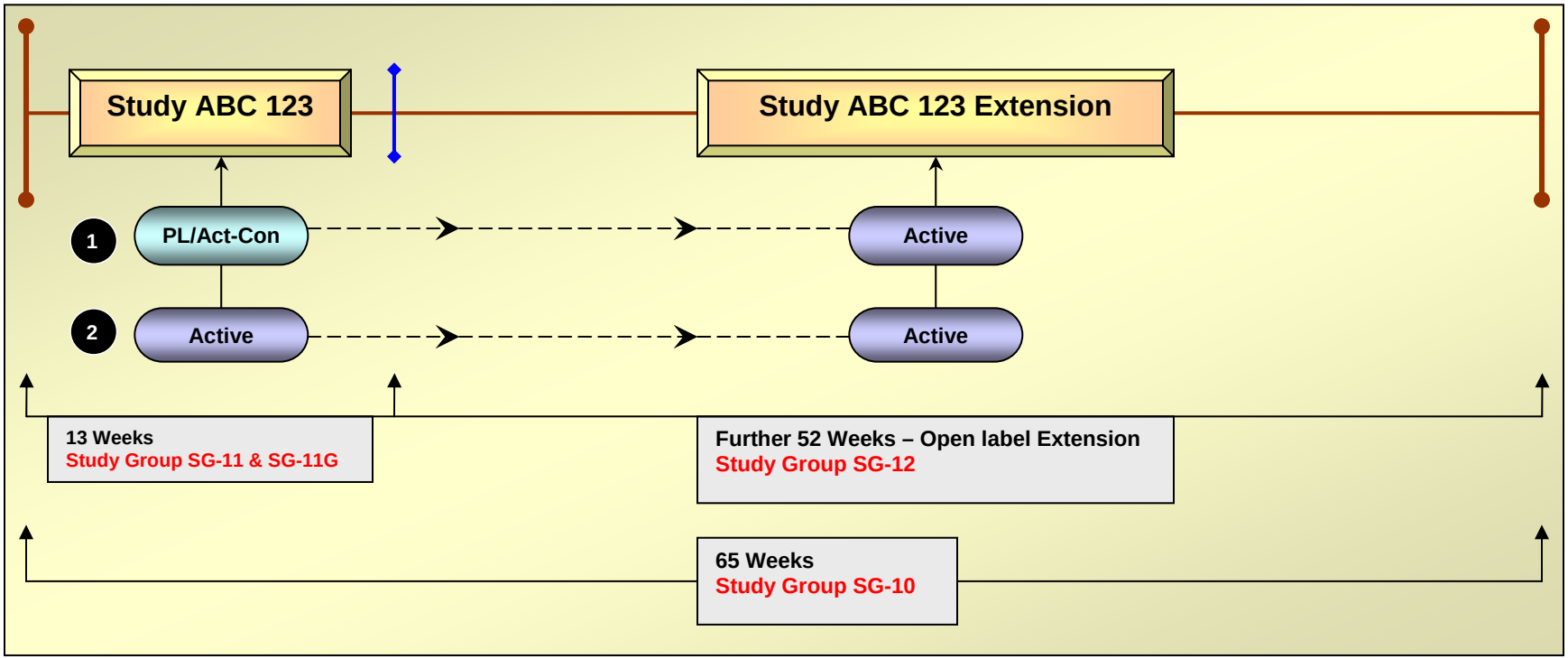
Although these were considered to be two independent studies, in actual fact, it was one (continuous) long-term study. This meant that a group of patients, who completed the parent study automatically enrolled to its extension phase where they were randomized and treated with the same IMP or a different IMP from the parent study. So the treatment exposure selection varied accordingly to the Study Group definition and Sub-Group definitions. Two examples are given below to demonstrate this:

1. A patient randomized and treated with different IMPs in both studies. As displayed in Figure 2 below
   - For study group SG-11 and SG-11G, the exposure will only include either Placebo (PL) or Active Control (Act-Con) Treatment
   - For study group SG-12, the exposure will only include Active Treatment
   - For study group SG-10, the exposure will include both Placebo and Active Treatment. Here, the patient was counted in more than one treatment group

2. A patient randomized and treated with the same IMP in both studies. As displayed in Figure 2 below
   - For study group SG-11 and SG-11G, the exposure will only include the first study i.e first 13 weeks of Active Treatment
   - For study group SG-12, the exposure will only include the extension period i.e 52 weeks of Active Treatment
   - For study group SG-10, the exposure will include the whole Active Treatment Period across both studies (13 + 52 weeks). Here, the patient was counted just once under the Active Treatment group

With the second example it was important that the patient was not double counted within the Active Treatment group. This was achieved by creating an algorithm within a macro program which matched its subject identifier value of the parent study with its extension phase and counted it just once within the Active Treatment group.

Figure 2



11. ADVERSE EVENTS

Adverse events were collected at each clinic visit, including follow-up visits/contact and were all recorded independently of severity or relationship to IMP. All AEs were categorized by System Organ Class (SOC) and Preferred terms (PT) according to MedDRA version 11.0. Only treatment emergent AEs were reported in the summaries for the ISS.

To integrate AE for studies that spanned over a decade, the coded terms for AEs were handled by having them re-coded in order to have uniformity. For this safety warehouse, AEs were re-coded by study, as appropriate, using MedDRA version 11.0. No further clarification was possible from sites so the data were reviewed by the same team to ensure consistency of approach. Both updated codes and the original codes were retained in the SDTM datasets.

The derivation of treatment emergent AEs across all studies was a challenging task due to diverse study designs which ranged from parallel (single-dose and multi-dose), open- label (OL), to cross-over studies (2 - 5 way). This was further complicated by the different follow-up periods being stipulated for the studies.

11.1 TREATMENT EMERGENT AEs

The more complex derivations for treatment emergent AEs were most noticeable for the Phase I cross-over studies where treatment emergent AEs would have to be associated with the treatment group in which they became treatment emergent – AEs which started during the washout would be associated with the treatment received immediately prior to the washout. The onset day of the event would associate to the start of the individual treatment phase instead of the start of the first dose. It was possible for an AE to be associated with more than one treatment if it increased in severity/seriousness/relationship following the start of study medication for the particular treatment.

For example, in a simple 2-way cross-over, placebo and active controlled, double-blind, single oral dose study, if an AE occurred at washout A, the event was assigned to Active A.

Run-in	**Active A**	**Washout A**	**Active B**	**Follow-up**

For studies with a placebo run-in or washout period, any AEs which started during the placebo run-in were not considered to be treatment-emergent and those AEs which became treatment-emergent during the placebo washout were assigned to the last Active Treatment received.

Placebo Run-in	**Active A**	**Placebo Washout**	**Active B**	**Placebo Washout**	**Active C**	**Follow-up**

In order to combat the complexity of the study design, a variable for the study day of the start of the AE was created to validate the derivation of the treatment emergent assignments. This variable provided an independent verification that the AEs were correctly assigned as treatment emergent AEs, since this variable was derived based on the first dose date of that treatment phase and not the overall treatment.

The complexities of treatment-emergent AEs were simplified by the use of relevant variables to verify the correctness of the derivations and the creation of dedicated macros programs separately for Phases I and II by combining studies with similar design.

12 BASELINE AND ENDPOINTS

12.1 VITAL SIGNS, LABS AND ECG

12.1.1 BASELINE DEFINTIONS

Before the integrated project commenced, most of the pivotal studies had already been reported with their individual Clinical Study Report (CSR). Hence as per the Sponsor's directive we initially followed the baseline definitions as per the CSR. But as we closely observed the data we found numerous discrepancies in the baseline definitions.

For some patients, it was evident that the time the laboratory tests were collected at the baseline visit (as per the CSR) was after the time of first intake of the IMP. Consequently the baseline definition was revised to be the last visit before the intake of first dose, taking the date and time into consideration when deriving the new baseline flag. This new flag was then used to identify the baseline result, instead of referring to a specific visit. The revised definition was approved by the Sponsor.

12.1.2 ENDPOINT DEFINITIONS

For labs, ECG and vital signs, we initially followed the global endpoint definition as the last post-baseline visit before the follow-up visit. As per Sponsor directive it was later changed to follow that in the individual pivotal studies. This resulted in varied definitions as follows:

- For each Vital Signs test it was the last non-missing post-baseline visit for each test
- For ECG and Laboratory test it was using the last non-missing on-treatment post-baseline visit

By applying the above criteria, in the case of Vital Signs, it meant that the data, where available, were not excluded and the outputs produced for the safety analyses indicated a consistent value in number of patients at Baseline and Endpoint.

CONCLUSION

As the project came to a close, there was a sense of satisfaction, relief and tremendous achievement as our sponsor successfully filed a CDISC compliant submission to the Regulatory Agency. The Programmers and Statisticians at Covance benefitted a great deal through the challenges associated with a large and complex data integration combined with application of CDISC standards. With this strong experience, the team is ready to take on more integration challenges of similar or greater magnitudes.

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