

# Preparing an eSubmission based on multiple trials, some of which are ongoing — challenges for statistical programming

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Preparing for an eSubmission based on multiple trials, some of which are ongoing, is a challenging task for statistical programmers. Having Analysis Data Model (ADaM) standards in place and maintaining a pooled data repository will facilitate the submission work on the data side. However, generating more than 1100 tables and figures for the Integrated Summary of Safety and Efficacy, involving a large team of biostatisticians and statistical programmers (in-house and off-shore), requires careful planning that includes preliminary discussions on consistency across programs. The purpose of this paper is to share experiences and provide some advice for statistical programmers to consider in future submission work.

**Keywords:** eSubmission, Standard, Repository, Validation, ISS/ISE

## Introduction

The work presented in this paper was carried out by the statistical programming group at Ferring in preparation for an eSubmission including one pivotal phase III trial, eight ongoing trials, and 17 completed phase II–IIIb trials. The phase IIIb trials, the majority still ongoing, were part of a previous submission of another formulation of the same product (FER123). Both ongoing and completed trials from the previous submission were to be included in the combined safety analysis of FER123.

## Data Standards

Ferring implemented analysis data standards in the beginning of 2009 based on the draft CDISC Analysis Data Model (ADaM) version 2.1.<sup>1</sup> The objective was to set a standard as close as possible to the draft ADaM version. After the initial implementation, the standard has been maintained for each new trial across all projects and therapeutic areas in Ferring. The implementation of the ADaM standard has been successful for Ferring and has shown clear benefits in terms of less customization of work, recognition between trials, and facilitating discussions with other functions. Besides the benefits from having one common standard in place, by implementing ADaM, the analysis data from individual trials are submission ready and easy to integrate in a repository database.

## Data Repository

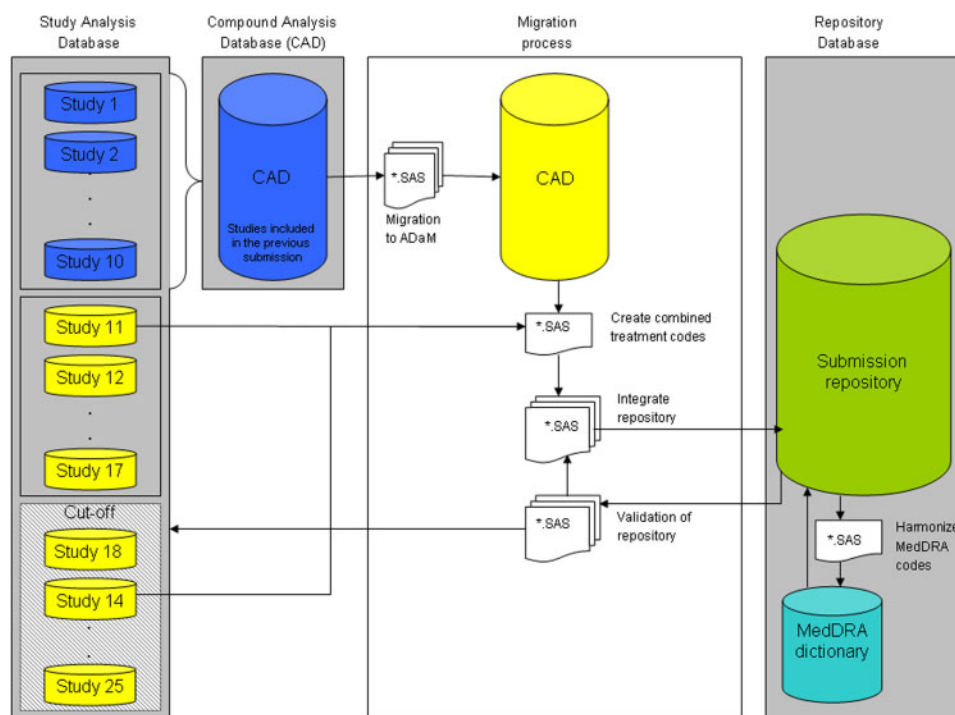
A legacy repository Compound Analysis Database (CAD) was built for the previous submission back in 2007. In 2009, the repository was remapped to the new ADaM standard in order to have the same structure across trials. The repository was continuously updated with new trials with the purpose to be used for safety updates to the regulatory authorities e.g. INDs and PSURs. The aim was to in the future extend the repository to also include efficacy data and hence be used for exploratory analyses.

For this submission, the current repository was updated to include the pivotal phase III trial and all new ongoing phase IIIb trials. Analysis data on primary and secondary endpoints (ADEF) were added and integrated in the repository for all trials since the submission required pooled efficacy analyses.

For the ongoing trials, a common database cut-off date was defined. The programmers created ADaM datasets for eight new ongoing trials which were appended to the repository. Each programmer was responsible for the set of programs generating ADaMs for a specific trial, even though one big batch file was used ultimately to run all programs and update the repository. All issues on a trial level were handled by the responsible programmer; however, communication within the team was necessary to guarantee that all programs were executed in proper order whenever the repository was updated.

Pooling the data across trials for the repository was a challenging task due to several factors, such as the lack of consistency in naming conventions for visit

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**Figure 1** Repository database design

structure (screening visit can be visit 0 or visit 1) and treatment codes (active 100 mg can be A or B). A major challenge for the repository was the streamlining of laboratory test codes and their associated units. Another complicating factor occurred when patients switched between treatments during a trial, which was important when considering the treatment allocation on the repository level.

Figure 1 shows the repository database design and the flow of trial data. Databases in sponsor format are indicated in dark grey and databases following ADaM standard are shown in white and light grey. The individual trials included in the previous submission were in different formats and were pooled in the CAD for the previous submission. The figure shows how the data are migrated from CAD and individual trials to one common repository by first harmonizing the treatment codes (ADTR), which is applied across all datasets.

### Validation and Cleaning

Data for ongoing trials often contain errors and even inconsistencies because they are incomplete and not fully cleaned. Ideally, data for ongoing trials should be kept as they are until cleaned according to normal routines. A validation of the repository is necessary to ensure consistency across trials, as well as to identify critical errors or missing data. In this process, the following issues needed to be handled before finalizing the repository for the submission:

- lack of coding for Adverse Events, Medical History, and Concomitant Medication;

- data errors in critical modules like exposure (ADEX) and subject level (ADSL);
- extra laboratory results performed on unscheduled visits;
- ‘reason for discontinuation’ not captured using the same standard in the eCRF across trials;
- missing ADaM datasets for individual trials, i.e. not required for reporting on the trial level.

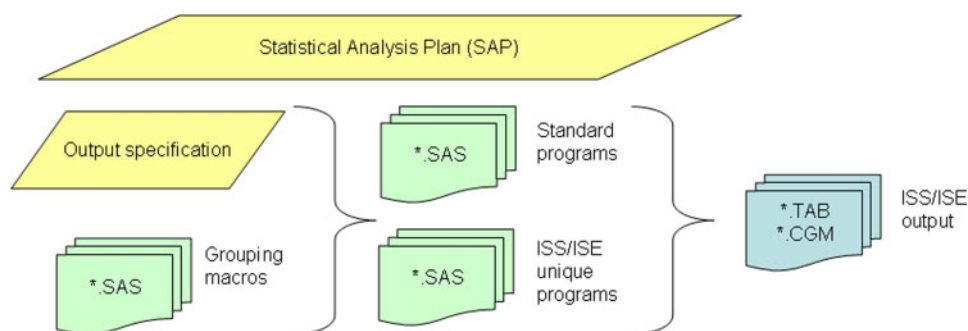
The validation findings were documented in a report that included the action to be taken by the responsible programmer, as well as timelines for completion. In this process, it was very important to communicate the necessary changes and to identify the persons responsible in order to solve each problem at the trial level; otherwise, ownership of findings would be unclear and lead to delays in the process.

The issues mentioned above might have complicated the programming and could have affected the presentation of the results; therefore, this step was regarded as critical.

*It is recommended to discuss expectations concerning data cleaning with trial managers and to agree on key data points prior to cut-off time.*

Coding of Adverse Events, Concomitant Medications, and Medical History for ongoing trials had not been completed at the cut-off date and, hence, the dictionary codes were added to the datasets at a later stage. Normally, the coding would have been accomplished long before the cut-off date.

The MedDRA codes for AEs were based on different MedDRA versions for the individual trials and this was harmonized on the repository level to use the latest MedDRA version across all trials (Fig. 1).



**Figure 2** Generating output

*It is recommended to afford adequate time for coding of ongoing trials after data cut-off in the submission timelines. The version of the MedDRA dictionary used for the pivotal trial and for the Integrated Summary of Safety (ISS) must be decided at an early stage.*

When all the validation comments were resolved and the pivotal phase III trial was included, the repository was considered final. Access rights were revoked and the submission repository was protected from further changes.

### Output Programs

More than 1100 tables and figures were produced for the Integrated Summary of Safety (ISS) and Efficacy (ISE). For this task, a team was formed including biostatisticians and several statistical programmers both in-house and off-shore. Careful planning of program set-up and structure, as well as upfront discussions on consistency across programs, ensured that all output programs were harmonized.

#### Program structure

Several 'Grouping' macros were used for generating tables and figures for different pooled trials (e.g. phase II/III/IIIb trials, phases II and III), and different doses/regimens and controlled/uncontrolled trials. The grouping macros were created and included across all output programs (Fig. 2). In the middle of the process of preparing programs for all outputs, the clinical team decided to change one of the groups (removed trials with short duration) defined in the Statistical Analysis Plan. Because the grouping macros were in place, this change was easily implemented by updating one of the grouping macros. Another benefit of these grouping macros guaranteed consistency with respect to titles and footnotes.

Ferring has developed standard programs for Adverse Event reporting and laboratory summaries. The standard programs were utilized for the ISS; however, submission-specific versions of these standard macros were created to cope with minor changes without interfering with normal daily trial work. Using these standard programs afforded a consistent workflow.

*It is recommended to include the possibility of presenting the output of multiple trials when developing standard programs for reporting in order to be able to use the standard programs for ISS/ISE. For example a demography table should be possible to represent more than one trial in the same output using a standard program.*

Figure 2 shows how the ISS/ISE outputs were generated with input from the output specifications (logic and design shells) deduced from the Statistical Analysis Plan definitions. Then, grouping macros were developed as prerequisites to be used in either standard programs or individually developed output programs.

During the output programming phase, different programming conventions, data handling issues, and program logics were discussed and shared within the programming team. Having pro-active programmers sharing experiences and thinking outside of their own program as well as communicating openly was important to achieve success.

#### Validation strategy

The program validation was not started until the full set of output programs had been completed by the programming team. This ensured that all general issues had been detected and resolved across programs before validation took place. An output review meeting was conducted by the clinical team, whereupon further adjustments were made, prior to program validation.

All programs were validated by a second programmer and three different levels of validation were applied in line with Ferring's procedures:

1. Level 1: a general check of the program code, check of output content (realistic numbers, cross-checks, etc.) and layout, consistency with specification, examination of the log. Level 1 is used for validating call of standard programs, listing programs, and ADaM programs, not including any derivations or other low complexity programs;
2. Level 2: includes Level 1 validation as well as execution of the code in interactive mode step by step. Level 2 is used for exploratory work where the specifications may be lacking or not extensive;
3. Level 3: double programming performed by another programmer plus Level 1 validation. Level 3 is used for all ADaM datasets including derivations,

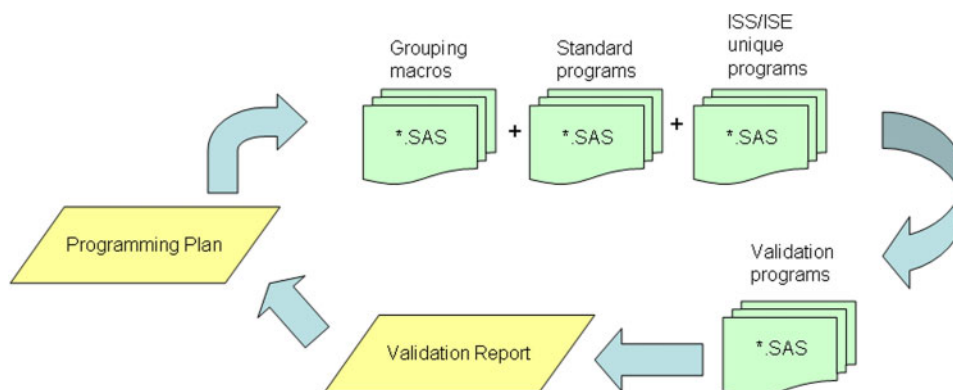


Figure 3 Tools for a structured programming approach

Status									
No	Title (shrinked)	Program	Output file	Programmer	Status	Validator	Date	Validation Level	Comment
1	Subject disposition	dispos	dispos	JAKE	Ongoing			3	
2	Demographics: Full Analysis Set	demoq	demoq (FAS,ITT)	JAKE	Ongoing			3	
3	Mean baseline parameters: Full Analysis Set			JAKE	Not Started			3	No data
4	Vital signs at baseline: Full Analysis Set	Vital	Vital FASFL	PETER	Draft	SARA		3	
5	Vital signs at baseline: Safety Analysis Set	Vital	Vital SAFETYFL	PETER	Draft	SARA		3	
6	Vital signs at baseline: Per Protocol Analysis Set	Vital	Vital PPROTFL	PETER	Draft	SARA		3	
7	Medical History of All events by MedDRA SOC	mh	T MH SOC MH F	PETER	Validated	SARA	2011-06-30	1	
8	Medical History of All events by MedDRA SOC	mh	T MH SOC MH S	PETER	Draft			1	
9	and PT - Safety	mh	T MH SOC MH P	PETER	Draft			1	
10	Concomitant Medication by ATC Classification	conmed	CONMED FASFL	PETER	Final	SARA	2011-06-22	1	
11	Level 1 and 2 - FAS								
12	Concomitant Medication by ATC Classification	conmed	CONMED SAFETYFL	PETER	Final	SARA	2011-06-22	1	
13	Level 1 and 2 - Safety								
14	Concomitant Medication by ATC Classification	conmed	CONMED PPROTFL	PETER	Final	SARA	2011-06-22	1	
15	Level 1 and 2 - PP								
16	Treatment compliance: ITT Analysis Set			PETER	Not Started			2	

Information on each item used to compile the output

Responsible programmer

Complexity (validation level)

Figure 4 Programming plan (ProgPlan)

primary endpoints, key secondary endpoints, and any complex or sensitive programs.

Before initiating the validation, the team discussed the overall validation strategy and determined the level of validation for each set of programs. Grouping macros and more complex programs were validated using Level 3. Most other programs were validated using Level 2 and some listings were validated using Level 1.

### Compiling the output

After all the output had been generated, a Word document containing a compilation of the process was included in the ISS/ISE documents. The ISS contained over 900 tables and figures, which was too large for Word to handle as one document. Discussions were

held with medical writers about how to split the output into multiple documents and how to number the tables and figures in the documents to ensure that proper referencing could be made in the ISS.

Special attention was given to verify that the compiled output fulfilled the requirements for the Ferring eCTD system with respect to PDF-size, templates, bookmarks, and hyperlinks. A test upload was conducted to check that the output documents were compatible with the eCTD system.

*It is recommended to discuss the format of the compiled output and to agree on numbering, subheadings, etc. with medical writers well before the final delivery.*

Table 1 Delivery timelines

Submission document	No. of TLFs≈	Time after DBL (week)
Pivotal phase III clinical trial report	500	1
ISE	200	2
ISS	900	3



## Data Format

Since the submission was going to the FDA, the data format and size of datasets needed to be aligned with the FDA eCTD specifications (Study Data Specifications 1.5).<sup>2</sup> Define files needed to be generated for the pivotal trial as well as for the repository for documentation purpose. To produce the Define files, a SAS program reading the ADaM specifications (metadata) from the Word file was created which automatically generated a Define file in PDF. Some adjustments to the ADaM specifications were needed where there were more programming instructions (SAS code) rather than a textual description of the logic for deriving the data.

The dataset format required by the FDA is SAS transport files (i.e. \*.xpt). According to the current FDA guideline,<sup>2</sup> the datasets can be up to 400 MB; however, the eSubmission system at Ferring has a limit of 100 MB. In fact, many of the repository ADaM datasets exceeded 100 MB, which had to be split into multiple files. For example, the laboratory domain (ADLB) exceeded 830 MB; thus, it was split into 10 files (ADLB1, ADLB2, ..., ADLB10). Moreover, splitting rules were implemented, such as: splitting by subject, site,  $x$  number of observations per file, etc. For this project, large data files were split by site in order to be aligned with what was generated by Data Management.

## Planning and Communication

The submission team of statistical programmers involved both biostatisticians and statistical programmers (in-house and off-shore). In total, 13 people were contributing with hands-on programming or validation for the submission including the pivotal phase III trial, the repository, and the ISS/ISE. About half of the 13 involved were working full-time with the submission and the others contributed with isolated parts during a shorter period. There were weekly meetings to discuss progress and issues, as well as to assign work, which was key to our success. At these meetings, strategies on how to deal with programming issues were discussed as well as any data complications that arose. These open discussions ensured that the team was well-informed and fully-aligned.

One statistical programmer and a project statistician were assigned to represent the team in discussions with the cross-functional team led by the regulatory team. Having a named resource assigned to this task ensured that communication between the regulatory team and the programming team was clear.

A programming plan (ProgPlan) was prepared to keep track of programs to be written, current status

(not started, ongoing, draft, validated or final), assigned programmer, and validator. In the ProgPlan, the level of validation required for each program was defined. The ProgPlan was kept up to date all the time and this was crucial for resource planning and to avoid obscurity of the responsibility of each individual. Similarly, a validation report was created to keep track of validation findings and actions taken. Tools such as the ProgPlan and validation report ensured a structured approach to the submission work (Fig. 3). An example of a ProgPlan is shown in Fig. 4.

Programming efforts for the full submission were grossly underestimated. Even worse, the effort to get the data into the repository turned out to be much more complex and time-consuming than expected. Fortunately, the programming for the pivotal phase III trial was started well in advance of the planned database lock (DBL). Preparation of the repository and ISS/ISE output was initiated 3.5 months before DBL for the pivotal phase III trial. During this time period, everything was prepared and at the time of DBL for the pivotal phase III trial, all the programs and the repository were in a very close to final stage.

The pro-active approach taken by the programming team led to the delivery times for all Tables, Listings and Figures (TLFs) (Table 1).

## Conclusion

To prepare for a submission based on multiple trials, some of which are ongoing, is a complex and challenging task for any statistical programming group. Utilizing the implemented ADaM standards, standard output programs, and maintaining a data repository, as well as front-loading of all output programs, enabled the Ferring team to complete the majority of the submission work in less than 4 months. Communication and planning as well as defining programming and validation strategies were key factors in preparing for the submission.

## Acknowledgements

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## References

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