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Using Workflows to Standardize Business Processes and Best Practices in Pharmaceutical Programming

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ABSTRACT

A best practice is a technique that has consistently shown results superior to those results achieved by following alternate techniques for the same objective. Business processes are a collection of activities designed to produce results for a particular objective. Workflow templates can be defined to combine these business process activities with the best practice techniques to be used as standards across an organization. The workflows can be used as instances of these workflow templates for the management of clinical data and programs. As clinical data is brought through the flow from data capture to analysis, it is frequently subjected to a workflow that enriches the data, un-blinds it or allows CRO's to add data elements to the complete set of trial data. These workflows make use of manual steps or involve complex processing steps that can use programmatic actions.

This paper describes how workflows can capture and enable several common business processes in clinical data management and development of statistical programs. In addition, it is demonstrated in technical detail how SAS Drug Development incorporates these workflows. Possible application areas of workflows in the pharmaceutical programming will be discussed, such as workflows governing the development of statistical analysis programs using good clinical practices and workflows for management of standards data exchange between a sponsor and the external partner (CRO). Workflows expose the pharmaceutical programs to a wide array of application areas and can be used as building blocks resulting in repeatable, validated complex processing jobs of clinical data and standards across therapeutic areas and trials. Finally, the workflow management system in SAS Drug Development contributes to optimizing the described business processes and allowing management to take fact-based decisions and optimize the conduct of future clinical trials.

BUSINESS PROCESSES, WORKFLOWS AND WORKFLOW MANAGEMENT SYSTEMS

BUSINESS PROCESSES

Business processes are a collection of activities designed to produce a specific output for a particular objective, possibly involving both human and system interactions.
A few examples of business processes in clinical trials:

- Development of statistical programs and the associated specifications process to release programs as part of a clinical trial programming submission effort
- Clinical data management staff, after capturing data from clinical sites and investigators, will query and clean the data and release it as clinical data domains to statisticians and medical staff.
- During exchange of data with external partners, pharmaceutical sponsors accept incoming patient data if they adhere to clinical data standards based on well-defined study and standards specifications

Each of those examples exemplifies specific business processes that are being used when collecting and analyzing clinical data in the context of a clinical trial analysis effort. These business processes are often described in quality documents and SOP's that are followed vigorously by the pharmaceutical company's employees. A lot of time is invested to train staff in these clinical departments to adhere to the SOP's and to keep them updated on latest changes. The ability and accompanying documentation to show that data has been managed according to business processes described in SOP's is called compliance.

WORKFLOWS

Workflows exist of a series of connected steps, whereby each step follows the start or precedent step and ends just before the next step begins. Each step consists of an activity that is assigned to one person, to a group of persons or is completed by a computer program. During clinical trial programming and data management activities, many business processes are in place and effectively being used to ensure that different tasks and activities are sequentially executed. What is important to note is that during translation of a business process in a workflow, a

literal translation of all activities during treatment of clinical data is avoided. The objective of workflow creation is to create an abstraction of all activities that balances control with flexibility to deviate from the specification if needed. In most cases this abstraction results in a simplification of reality.

WORKFLOW MANAGEMENT SYSTEM

A workflow management system is a computer system that ensures that each of the steps in the workflow are surfaced to the right individuals or groups, and that automated actions are executed at the right time and when the necessary conditions, as defined in the workflow, are fulfilled. Workflow management systems have been used before in clinical trial operations to follow up on trial progress, patient recruitment or clinical site monitoring activities, but their use in the activities governing clinical data management and statistical reporting is not common. A crucial requirement for a workflow management system used for clinical trial programming is that it is closely integrated with SAS programming activities in the same software system, so that the programs can be used as building blocks for triggering actions, or monitoring the progress of trial programming activities.

SAS Drug Development is the leading clinical software solution that provides a secure, global access to a centralized clinical information repository for all authorized clinical development team members. SAS Drug Development provides flexible yet rigidly controlled process workflows that enable the different described stakeholders to control the data and metadata at appropriate moments during the process. These process workflows can be consuming the stored data and libraries, and can be defined to automatically trigger SAS programs as a result of specific actions, such as the upload of new clinical data by a CRO into the system.

WORKFLOWS IN PRACTICE : 2 USE CASES

We describe two uses cases where workflows have been applied in clinical data management and statistical programming. Both use cases show how common business processes are translated in workflows and will be used later as examples to discuss more detailed aspects of workflows in SAS Drug Development.

USE CASE 1 : LIFE CYCLE OF A STATISTICAL PROGRAM

A rigorous life cycle of a statistical SAS program is deeply embedded and in most cases even enforced by validation procedures in the practices of the clinical programming community. In summary, it consists of using programming and business specifications to create a new data management or statistical program, and test it against some pre-agreed outcomes. This latter acceptance process is often done by transferring the program to an acceptance programmer who executes the test programs or test units (see for a robust technical approach using unit testing in SAS; reference 1**)**. If the program meets the specifications and the SAS log is error-free, it can be moved through and considered as part of the production environment (use case 1a; Figure 1). A variation of this use case is to have two programmers create the program, and then compare if they produce the same output – this is called double programming (use case 1b).

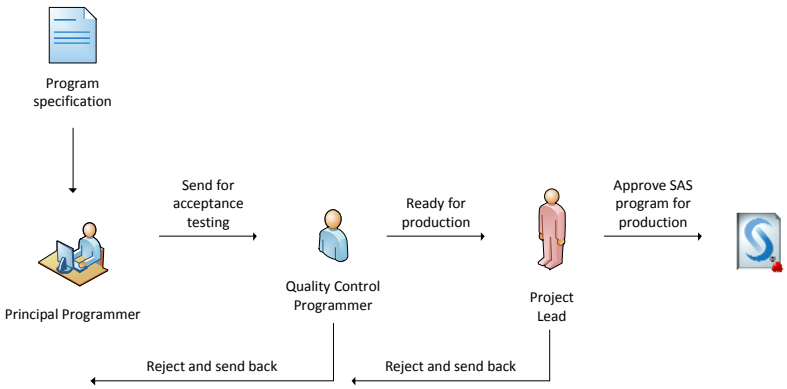

Figure 1 : Workflow representing program validation cycle

USE CASE 2 : A WORKFLOW GOVERNING THE EXCHANGE OF CLINICAL DATA BETWEEN SPONSOR AND CRO

One of the transformations and changes clearly taking place in the industry is a renewed definition of clinical data operations, data management and submission-driven activities including collaboration with external organizations. Many pharmaceutical companies are responding to this new environment by setting up collaboration models with external clinical data management partners based on strong data standards governance processes. These companies use SAS Drug Development to first specify data specifications by sponsors to CRO's and to check the

quality and adherence of incoming CRO data against the data standards and study specification libraries of the sponsor (see for an extensive discussion on this topic in reference 2). The user profiles involved in this process are the CRO user, the pharmaceutical sponsor's data manager and eventually other implicated groups such as PK/PD users and laboratory data providers. We are using the second part of this business process as an example of a workflow whereby the quality control of incoming standards data provided by the CRO is automatically triggered.

A business process can be added to SAS Drug Development to manage the quality control of the data and metadata uploaded by the sponsor to the platform. This comparison of incoming data (SDTM domains) and metadata (define.xml file or SAS tables containing the equivalent metadata) are used to firstly compare against the pre-defined study specifications and secondly against the organization's data standards, often based on CDISC (Clinical Data Interchange Standards Consortium) standard data models. This workflow is an example of a more complex template because it consists of both manual tasks and automated SAS job runs, and it contains a decision point that leads to two different branches in the workflow. The steps include;

1. Open up permissions for data upload
2. Send notification to CRO to upload data
3. Run automated SAS jobs to validate data
4. Generate and distribute validation reports to all
5. If fail return task to CRO
6. If pass, return task to promote data into study area

This workflow allows pharmaceutical organizations to (partially) reduce their interactions with CRO's in the context of specific trials and where pre-agreed data standards are used. It also increases the downstream interactions and produces a traceable and auditable record of the outcome of the comparison process.

WORKFLOWS IN SAS DRUG DEVELOPMENT

Workflows in SAS Drug Development are delivered through web services called the SAS Workflow services in the Middle Tier Architecture in the SAS Web Infrastructure Platform. Full documentation about the SAS Workflow service can be found in reference 3**.** In SAS Drug Development, the workflow management system surfaces to the user as work items (i.e. workflows) or automated SAS jobs. Work items consist of a user task or a set of tasks. In SAS Drug Development, a work item describes a unit of work that needs to be accomplished. For example, a work item can be defined to write code for a data transformation, safety report, or tables, figures and listing program. A work item needs to be defined in a workflow template which captures the tasks and process describing a best practice. A work item is a specific instance of a workflow, and many instances can be created in an instance for different contexts such as projects, analyses or organizations. A work item can have descriptions, due dates for tasks, assignees, the work or deliverable to is to be completed, the steps to take to complete the task, messages to send out at different transition points, and can link into the specifications document of the task at hand. Also, as soon as the work item is activated in the system, tasks can be re-assigned to other users when the assigned user is absent or if the workload becomes too big for the assigned resource.

CONFIGURATION OF WORKFLOWS IN SAS DRUG DEVELOPMENT

Workflows are configured in SAS Drug Development using the following process ;

- A visual layout of the business process is created by a business user. The visual layout of the process is translated into a technical workflow template. A workflow template is the specification of the workflow in a technical format that is understood by the SAS Workflow services. These templates can be parameterized so that they can be generalized for use in different clinical trials or projects.
- The workflow template is added to SAS Drug Development by a process called "workflow template activation" and new workflow instances can be copied in SAS Drug Development using this template ("workflow instantiation").
- Instances of workflows are working copies of the templates that are used in the context of a clinical project, trial or analysis and that are stored in the metadata of SAS Drug Development. When a workflow instance has been started by a user, the first work item is created and the parameters of the workflow have been resolved.

Once a workflow has been activated in SAS Drug Development, interactions with the workflow can be driven by a user ("user-application launch"), an external event ("signal-driven launch") or executed by an external third-party application ("services-driven launch").

WORK ITEM DEFINITION

For simple deliverables, the description field of the work item itself may be sufficient to detail the work to be accomplished. For more complex work items, attachments can be added providing more details, such as a program specification. The next step in defining a work item is to select the appropriate workflow. The workflow selection determines the flow and order of the tasks for the work item. For example, in Figure 2, a sample workflow is shown, reflecting the described use case 1a with a development, test and production step ("Dev/Test/Prod Workflow") as part of moving a statistical program into a productive clinical trial programming environment.

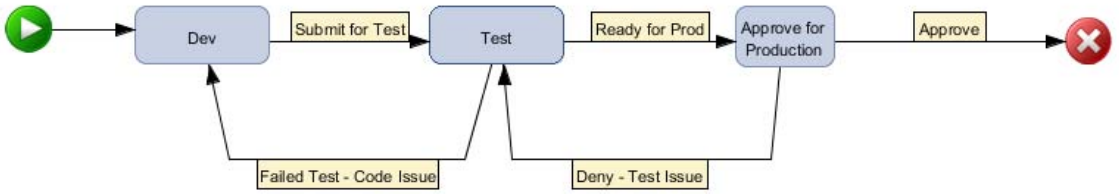

Figure 2 : Dev/Test/Prod Workflow

This workflow has three tasks which need to be assigned and completed, Dev, Test, and Approve for Production. This is an asynchronous workflow, where only one task is active at any given time.

WORK ITEM TASK ASSIGNMENT

Each of the tasks in a workflow can be defined as a User type task or as a Group type task. A task defined as a task type of User, is a task to be performed by an individual user. This type of task can be assigned to and individual or a group of users. When a User type task is assigned to a group, any individual within that group can claim the task to work on. For a Group type task, the task must be assigned to a group. In this case, any member of the group can work on the task without claiming it, and any member of the group can mark the task as complete. In the Dev/Test/Prod example above, the Approve for Production task might be defined as a Group task and assigned to a group of project leads. Any one of these leads can promote the program into production.

WORK ITEM TASK FLOW

Once the task assignments are designated, the work item can be started, triggering the tasks in the order defined in the workflow. To transition from one task to another, the task assignee, selects from a list of completion status values which were defined in the workflow template. In the Dev/Test/Prod workflow shown above, the transitions for each task are:

- Dev task
  - Submit for Test
- Test task
  - Ready for Prod
  - Failed Test – Code Issue
- Approve for Production task
  - Approve
  - Deny-Test Issue

In this case, the work item remains active until the completion status of Approve has been set.

Workflows can include activities or tasks which can be worked on simultaneously. Figure 3 shows a double programming example (referring to use case 1b).

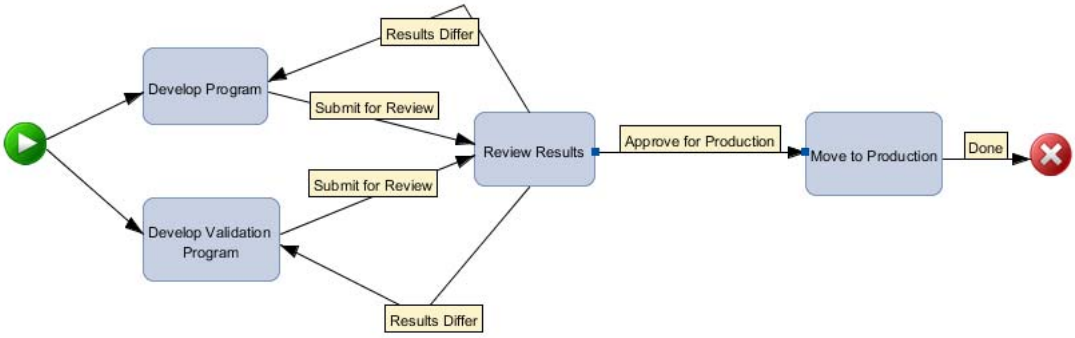

Figure 3 : Parallel Programming Workflow

In this case, when the work item is started, two tasks are triggered to be started, Develop Program and Develop Validation Program. The Review Results will not be triggered until both of the initial tasks have been completed and the status changed to Submit for Review. If the review finds that the results of the two programs differ, then the reviewer assigned to this task will mark the completion status as Results Differ. In this case both the Develop Program and Develop Validation Program tasks are re-activated.

USING AUTOMATED TASKS IN WORKFLOWS

In addition to tasks which are performed manually by a user, SAS Drug Development provides two types of tasks which are automated. These automated tasks are a Notification task and an Execute Job task. These tasks are assigned to the system, and will not appear in the task list of any of the users included in the workflow. A Notification task will send a notification message to all of the users identified in the notification task properties. Figure 4 shows the properties for a notification task.

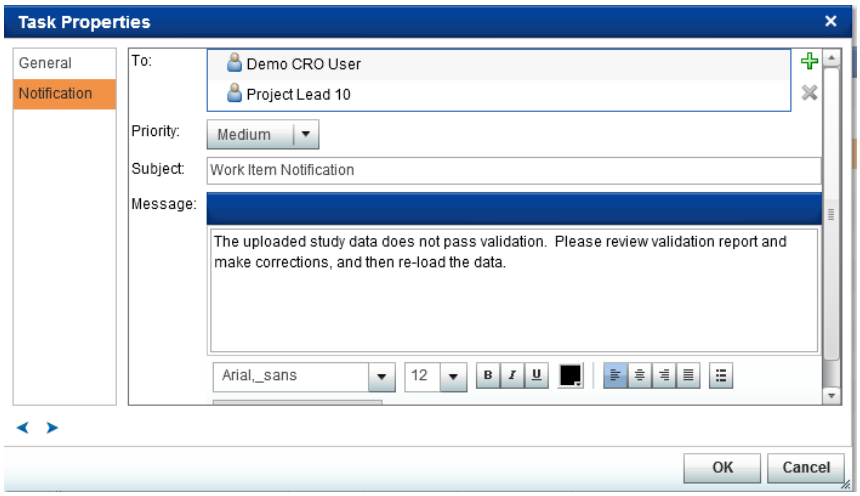

Figure 4 : Automated Notification Task Properties

The properties for this task include the list of users who should receive the notification as well as the content of the message. An Execute Job task will execute a SAS Drug Development Job and return the execution status of the job to the workflow. Figure 5 below shows the properties for a execute job task.

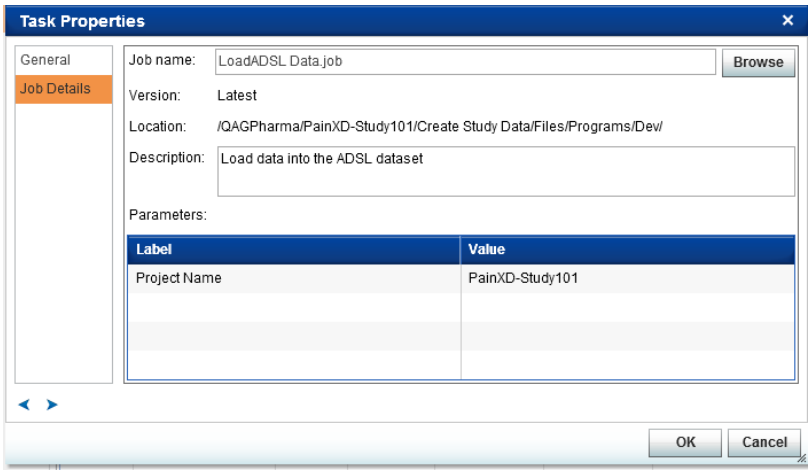

Figure 5 : Automated Execute Job Task Properties

Figure 6 shows a sample workflow reflecting use case 2 ("a workflow governing the exchange of clinical data between sponsor and CRO") which utilizes the automated notification and job execution tasks. In this example, there is a manual user task, to upload study data. When this task completion status is marked as Data Ready for Validation, a SAS Drug Development job is automatically executed. This SAS Drug Development job can be 1 or many SAS programs that can be executed in SAS Drug Development, and in this case the job checks whether the incoming study data adheres to the study specification and organizational standards. If the job is successful, then a notification is automatically emailed to the selected recipients. If the job fails, or results in SAS errors, then a failure notification is emailed to the selected recipients, and the manual task of uploading data is re-activated.

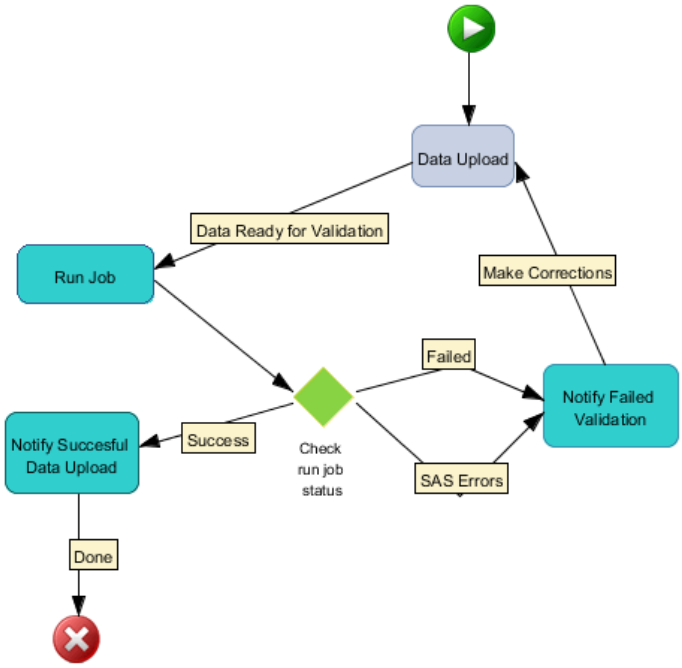

Figure 6 : workflow governing exchange of data between sponsor and CRO

CONCLUSION

We have shown here how the workflow management system in SAS Drug Development is uniquely equipped to embed business processes into technology to produce and execute the different tasks and jobs. While it should be clear that not all business processes can be captured in workflows, even partially automated processes are more efficient than completely manual processes. Advantages of workflows during clinical trial data management and analysis are standardization of processes and automation of actions and follow-up of tasks that take too long or have expired. SAS Drug Development also allows for sending out notifications to users and project leaders and this connects the programming department with the clinical users at a clinical development department.

During the processes that govern clinical data management and analysis, workflows can intervene to ensure that the different tasks are being executed, and allow management at pharmaceutical companies to follow up on progress. While the operational and transactional follow-up of trials is important, an important side effect of workflows becomes apparent : the ability to gather detailed metrics on key processes in order to fix bottlenecks and inefficiencies. Therefore workflows are configurable in SAS Drug Development and new workflow templates can be added over time leading to the need of a workflow life cycle. Good examples of these retrospective metrics can report on;

- the number of times a CRO has uploaded clinical data of a specific trial or project and the number of iterations to solve potential data issues.
- why certain categories of statistical programs are consistently rejected for acceptance
- tasks that take up the most time in a trial, i.e. where can more programming resources be added to speed up trial submission ?

Workflows are being added to SAS Drug Development as a capability at a time when clinical data standards are becoming embedded in the daily activities of the data manager and statistical programmer. CDISC standards enforce not just standardization of data processes, but better re-use of standard programs and macro libraries, and allow organizations to more easily exchange data (SDTM domains) and metadata (study specifications, define.xml) with CRO's and licensing partners on the basis of these standards. In this context, workflows are to be seen a layer above the CDISC data and metadata and the according SAS programs. Perhaps in due time a number of standard workflows will emerge in this context of dealing with CDISC-adherent data.

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3. SAS® Workflow Studio® 1.2: User's Guide, http://support.sas.com/documentation/onlinedoc/workflow/, 2012, SAS Institute

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