

PP15: Efficient Integration Programming Techniques

Authors: Vaibhav Sathe (Vaibhav.sathe@takeda.com), Aparna Polisetty (aparna.polisetty@takeda.com), Crystal Alvarez (crystal.alvarez@takeda.com), Mekhala Acharya (mekhala.acharya@takeda.com)

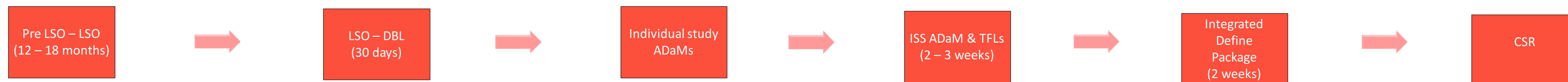
Background

With increasing complexity in clinical study designs, efficient integration analysis is critical to reduce cycle time. Although this analysis is common, the information around Integration planning is limited.

SDTM vs ADaM integration strategy

- Integrated Summaries of Efficacy and Safety are frequently submitted to regulatory agencies. These summaries usually pertain to a single drug component but can include data from multiple studies across various treatment schedules, which leads to complexity during integration.
- There are two main strategies for integration based on availability of source data: Utilize SDTM from individual studies to create integrated ADaM or integrate individual ADaMs directly. ADaM integration is preferred over SDTM.

Planning



Pre LSO – LSO period

- RACI creation
 - Roles and responsibilities should be clearly defined for all functions. Sample table shown below on how it outlines tasks, and RACI for both stats and programming team for all associated tasks such as integrated SAP, mock shells, ADaM, TFL programming and reviews.

Task(Integration)	STAT	Programming
iADaM spec creation	C	A/R
iADaM Spec review	R	A
iADaM creation	C	A/R
iADaM QC	I	A/R

R: Responsible, A: Accountable, C:

- **Strategy and planning**
 - Detailed early planning of Timelines and identification of key milestones is required. This includes integrated SAP and TFL mock shells creation, receipt of study level AdAM datasets, AdAM and TFL programming, Define package creation, P21 compliance runs, iADRG, and final delivery.
 - A well aligned Escalation plan is in place when issues arise with data, timelines and performance.
 - Early identification of resources with ample time for early cross-functional team reviews of integrated SAP, shells, AdAMs & TFLs and, Define package.
 - An Early and a Late dry-run is planned to ensure all issues are resolved prior to DBL.
 - Thorough reviews including programming oversight, stats, and cross-functional team are planned to ensure any issues are identified early.
 - While doing ISS analysis, we up-version dictionaries and plan for this as early as possible.
 - Before programming ISS AdAMs, the integration strategy is defined to include study windowing rules, analysis rules relevant to integrated SAP and Protocol, and statistical methods. Any gaps identified in available data are communicated with Statisticians and individual study Leads for reconciliation.
 - The Standardized Tracker is used which includes tabs for tracking programming activities, tracking time-off, resourcing and for identified data issues. Additionally, a dashboard (as shown below) is included to give snapshot of current status.

A2HAM						
Total Number	Production Ready	QC Passed	QC Failed	Stat Passed	Stat Failed	
3	0	0	0	0	0	0
A2HAM Progress Roster						
Production Program	Number of Programs Assigned	Number of Programs Completed	Percent Completed	QC Programmer	Number of QCs Assigned	Number of QCs Completed
HCALC1	0	0	RDY/0%	HCALC1	0	RDY/0%
					4	0
A2HAM Progress Roster						
Production Program	Number of Programs Assigned	Number of Programs Completed	Percent Completed	QC Programmer	Number of QCs Assigned	Number of QCs Completed
HCALC1	0	0	RDY/0%	HCALC1	0	RDY/0%
					4	0
A2HAM Progress Roster						
Production Program	Number of Programs Assigned	Number of Programs Completed	Percent Completed	QC Programmer	Number of QCs Assigned	Number of QCs Completed
HCALC1	0	0	RDY/0%	HCALC1	0	RDY/0%
					4	0

- **Integrated SAP & mock shells**
 - Early engagement with stats which involves review of the integrated SAP and ensuring Mock shells are consistent with analyses requested in integrated SAP and providing suggestions /comments.
 - Integrated SAP must be carefully reviewed by the programming team to unambiguously construct analysis data sets and prepare planned TFLs.
 - Integrated SAP should also contain study specific details of the individual studies required to be integrated.
 - Review the mock shells to ensure they adhere to company specific standards.
 - Schedule regular meetings with stat to discuss any issues arising from data that impact analyses, seek guidance in handling reporting data.
 - Programming team should request statistician to have all updates agreed upon, to be reflected in the integrated SAP.
 - Annotated TFL mock shells are created to reduce turnaround time.
- **Programming**
 - Early dry-run of outputs, development of iADRG, and Define.xml to ensure final submission packages can be produced within 2 weeks after final integrated TFLs are completed.
 - Ensuring that AdAm specifications are always kept up-to-date to reduce re-work later during define package finalization.

Pre LSO – LSO period (continued)

- Ensuring that all outputs part of submission package have gone through at least one round of dry-run prior to LSO.
- Ensure CDISC compliance of integrated ADaMs using P21 for every formal deliverable.
- Post Database lock, finalization of final TFL package within 3 weeks for Base case scenario and within 2 weeks for Best case scenario.
- We have developed a QC checklist (snippet is shown below) to guide production and validation programmers on all the checks required to be completed prior to any formal deliverable.

AdAM		
Make sure all needed variables based on TLFs are present in respective <i>AdAM</i> datasets	Yes	No
Ensure that check log macro is <i>run</i> and issues addressed for AdAM	Yes	No
Variable names, labels, formats (as applicable) match what is in the specification	Yes	No
Follow <i>AdAM</i> specs to QC <i>AdAM</i> datasets using double programming approach	Yes	No
Review QC the specs and raise concerns to both Prod programmer and Lead	Yes	No
Ensure the observations in dataset report in correct order (starting usually by treatment, subject, visit, date). Check if duplicates records are present in the data.	Yes	No
Check P21 report and see if production programmer feed all programming related updates as per P21 report.	Yes	No
Make Prod programmer and Lead aware of any sharp increase in number of observations. Source vs SDTM vs <i>AdAM</i>	Yes	No

TFLs	
Ensure that check log macro is run and issues addressed for TFLs	Yes ☐ No ☐
Was Programming Validation added per footnotes (TOOL-0013796)	Yes ☐ No ☐
Appropriate hyperlinks are added in footnotes section for the references in column labels	Yes ☐ No ☐
Types in the table have been rectified.	Yes ☐ No ☐
TFLs are compared with the study Mock files to make sure they are 100% matching.	Yes ☐ No ☐
There is no truncation of text in any part of the table such as titles, footnotes, or at data within the table.	Yes ☐ No ☐
If applicable DATE formats and date text case is consistent throughout the table	Yes ☐ No ☐

LSO – DBL period

- Perform final data cleaning activities.
- Late dry-run
 - Get confirmation from individual study teams that the updated ADaM datasets received are CDISC compliant.
 - Ensure all previously raised issues with respect to data or ADaMs are resolved with this final pre-DBL transfer.
 - Perform a late dry-run and cross-functional team review.
 - Plan with late dry-run is to clear out any issues with programs / output layouts up-front and reduce the time post DBL.
- Performing a test run at individual study level using blinded (dummy) randomization file to ensure unblinding process will go smoothly.

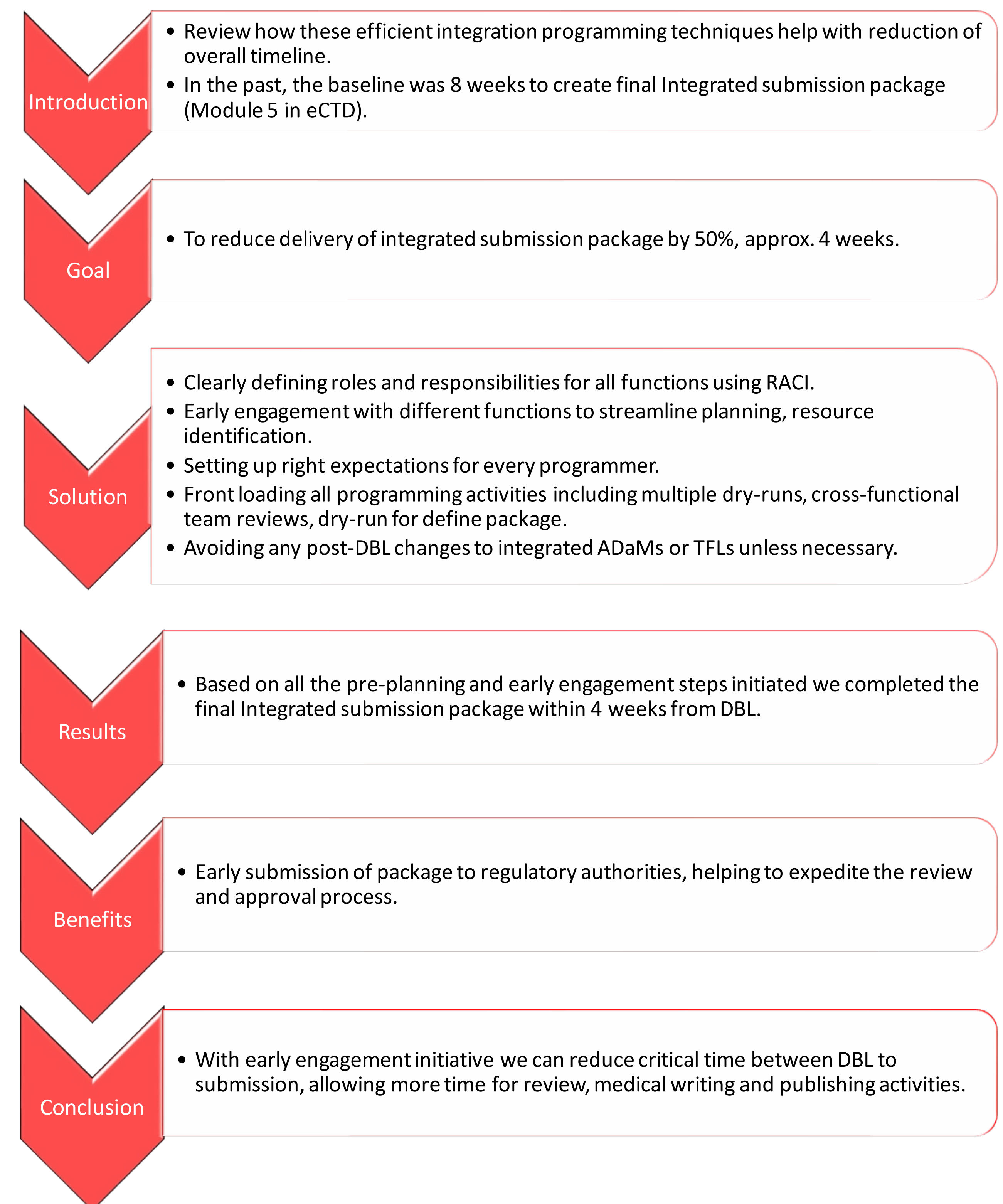
Individual study ADaMs

- Wait to receive individual study final ADaM datasets post-DBL.
- Ensure completeness of individual study level ADaMs and that appropriate level of unblinding has been performed as applicable.

ISS ADaMs & TFLs / Define package

- Post-DBL timelines are developed as both Base case and Best case scenarios to prepare for any unknowns.
- Base case timelines are to be met for every study. Best case scenarios are aspirational and driven by automation and quality assurance of data and code reviews.
- Base case scenario: ISS Final TFLs 3 weeks after Pivotal study CSR final TFLs (one week for draft ISS pooled ADaM/TFLs, one week for cross-functional team review, one week for final ISS ADaM/TFLs).
- Best case scenario: ISS Final TFLs 2 weeks after pivotal study CSR final TFLs.
- Draft ISS ADaM & TFLs to be ready within 1 week from receipt of individual study ADaM datasets.
- Perform statistics and cross-functional team review and finalize ISS datasets and outputs within 3 weeks from receipt of individual study ADaM datasets.
- Define package creation & finalization within 2 weeks post ISS TFL finalization.

Case Study



Abbreviations: ISS – Integrated Summary of Safety, LSO – Last Subject Out, DBL – Database Lock, SAP – Statistical Analysis Plan, TFL – Tables, Figures, and Listings, SDTM – Study Data Tabulation Model, ADaM – Analysis Data Model, iADaM – Integrated ADaM, P21 – Pinnacle 21, CDISC – Clinical Data Interchange Standards Consortium, iADRG – Integrated Analysis Data Reviewer’s Guide, eCTD – Electronic Common Technical Document