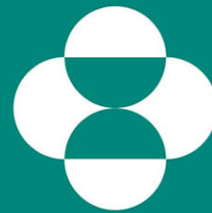


Analysis Package e-Submission – Planning and Execution



MERCK

INVENTING FOR LIFE

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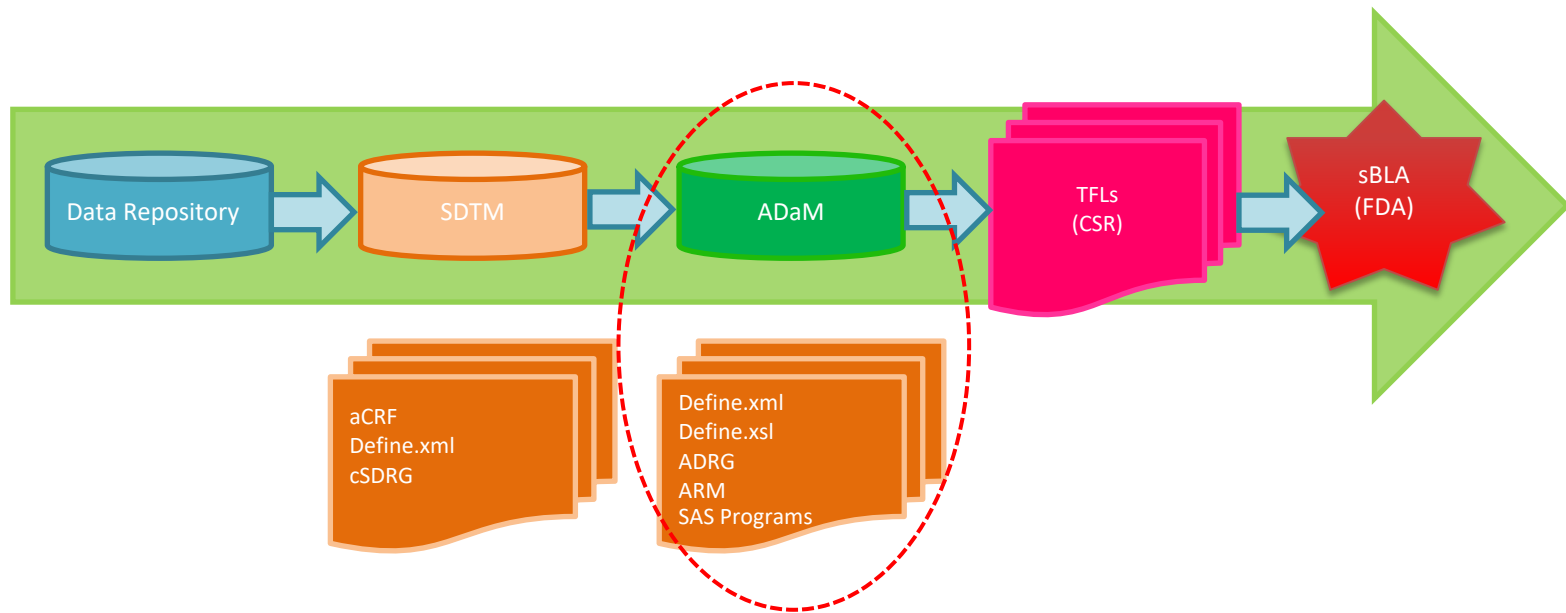
Agenda

- Introduction
- Analysis Package Components
- Challenges
- Solutions
- ADaM CoE
- Conclusion

Introduction

- Analysis package
 - One of the main components of CDISC based e-submissions
 - Stakeholders involved
 - Cross functional teams collaboration
 - Planning and timelines
 - Creation Process, challenges and solutions
 - Useful tools

eSubmission Process Overview



Analysis Package Components

- Datasets (XPTs)
- Define.xml
- Define.xsl
- Analysis Data Reviewers Guide (ADRG)
- Supplemental Data Definition (Optional)
- Analysis Results Metadata (ARM)
- Programs

Challenges

- **ADaM Data Specifications**
 - Not matching actual data
 - Spelling mistakes
 - Incorrect or incomplete derivation
 - Lack of details for the derivation
 - Not using latest template
 - Special characters in ADaM specifications
 - Parameter Value Level Metadata
 - Lack of inputs from validation programmer or reviewer (statistician)

Solutions

- **ADaM Data Specifications**
 - Utility macros and automation
 - Data set attributes, variable order, check for key variables, carry forward core variables etc.
 - Identify special characters
 - Thorough review process
 - Developer programmer, validation programmer, statistician
 - Relevant stakeholders
 - Central repository (Ex: SharePoint website)
 - Company specific adaptor in Pinnacle 21

Challenges

- **Datasets**

- Not following ADaM principles
- Issues identified by running Pinnacle 21 late
- Special characters in datasets
- Consistency between SDTM and ADaM
- Consistency within ADaM datasets
- Last minute changes to ADSL
- Datasets with complex derivations

Solutions

- **Datasets**

- Official CDISC ADaM training, ADaM implementation kickoff meeting
- Multiple iterations of Pinnacle 21 validation before DBL and final run after DBL.
- Pinnacle 21 and sponsor specific tools
- Second subject level dataset (ADBASE)
- Intermediate ADaM datasets

Challenges

- **Tool (Pinnacle 21)**
 - Knowledge and Usage
 - Adapting to newer versions
 - Interpretation of issues
 - False positives
 - Creating ADaM Define
 - Access control and naming conventions

Solutions

- **Tool (Pinnacle 21)**
 - Adequate Trainings
 - Issue log documentation, FAQs
 - Company specific Adaptor to create a define.xml from ADaM spec
 - SOPs and Execution Resources

Challenges

- **Coordination between multiple teams and efficient communication**
 - Explaining the ADaM Principles to different functional groups
 - Communication pathway to different groups regarding issues related to ADaM datasets
 - Resolutions of data issues and documenting issues that can't be resolved in ADRG
 - Consistent approach within programming groups

Solutions

- **Coordination between multiple teams and efficient communication**
 - Regular meetings
 - Sharing lessons learned
 - Communicating new updates
 - Discussions regarding ADaM Principles
 - Getting answers for FAQs
 - Provide standard text for issues that can't be resolved
 - Standard templates, SOPs, Execution
 - SharePoint websites

Challenges

- **Review Cycle**
 - Multiple stakeholders
 - Coordination and time to review
- **ADRG**
 - Including right amount of information
 - Rationale for issues that can't be resolved
 - Consistent format (document sections etc.)
- **Analysis Results Metadata (ARM)**
 - Identifying Key Analysis Results
 - Gathering Metadata information

Solutions

- **Review Cycle**

- Establish Review and update timelines

- **ADRG**

- Standard Templates
- ADRG completion guidelines
- Include key points and important information

1. Introduction
 - 1.1 Purpose
 - 1.2 Acronyms
 - 1.3 Study Data Standards and Dictionary Inventory
 - 1.4 Source Data Used for Analysis Dataset Creation
2. Protocol Description
 - 2.1 Protocol Number and Title
 - 2.2 Protocol Design in Relation to ADaM Concepts
3. Analysis Considerations Related to Multiple Analysis Datasets
 - 3.1 Comparison of SDTM and ADaM Content
 - 3.2 Core Variables
 - 3.3 Treatment Variables
 - 3.4 Subject Issues that Require Special Analysis Rules
 - 3.5 Use of Visit Windowing, Unscheduled Visits, and Record Selection
 - 3.6 Imputation/Derivation Methods
4. Analysis Data Creation and Processing Issues
 - 4.1 Split Datasets
 - 4.2 Data Dependencies
 - 4.3 Intermediate Datasets
 - 4.4 Variable Conventions
5. Analysis Dataset Descriptions
 - 5.1 Overview
 - 5.2 Analysis Datasets
 - 5.2.xDataset – Dataset Label
6. Data Conformance Summary
 - 6.1 Conformance Inputs
 - 6.2 Issues Summary
7. Submission of Programs
8. Directory Structure

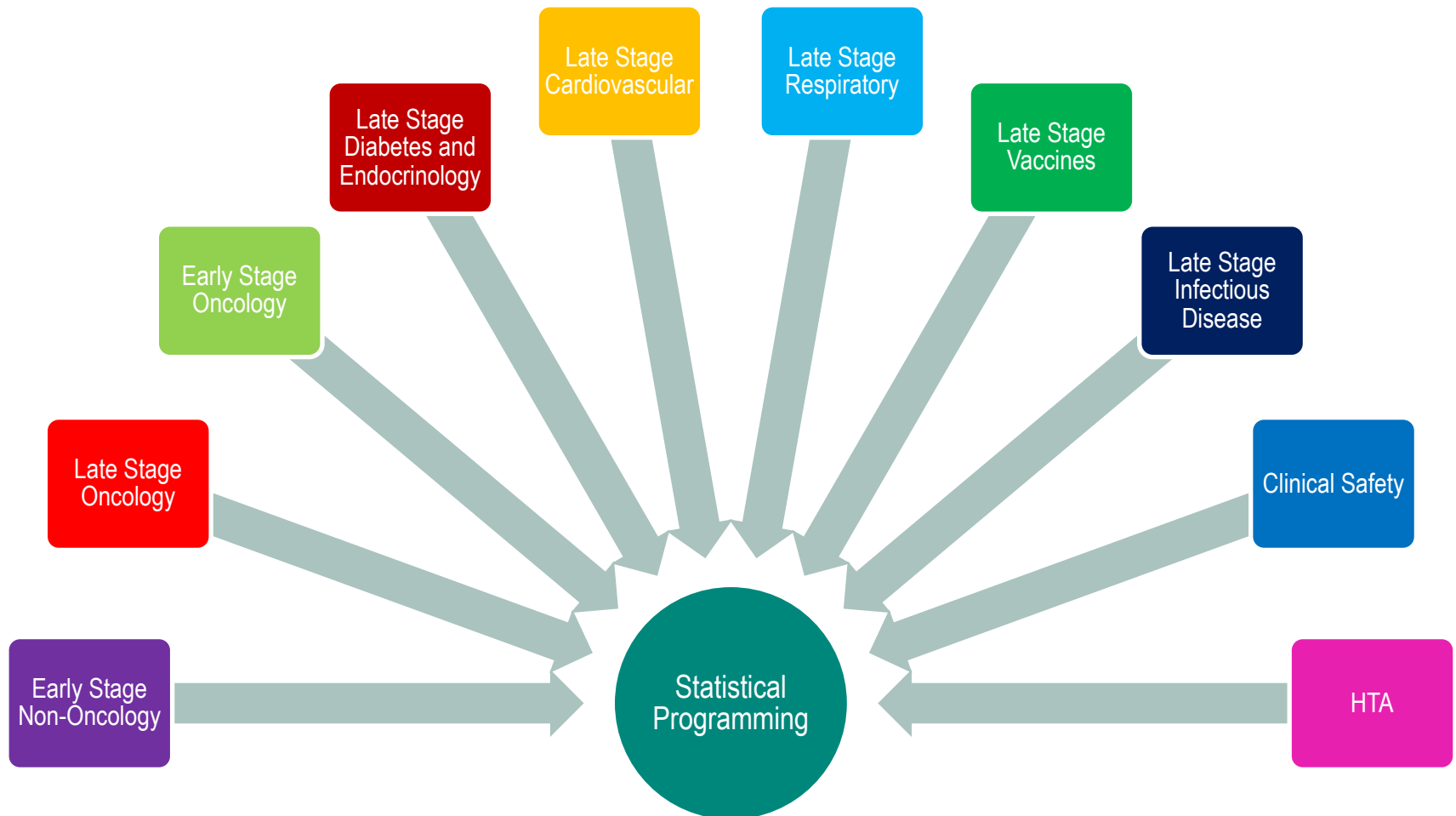
Solutions

- **Analysis Results Metadata (ARM)**
 - Identify key study endpoint analysis
 - Collaboration between statistician and programmer

3. Analysis Results Metadata Details

Table Reference:	
Analysis Result	<i><include analysis result of interest></i>
Analysis Parameter (s)	<i><add useful parameters that is the focus of the analysis result></i>
Analysis Variable (s)	<i><include specific variables that will be analyzed></i>
Analysis Reason	<i><define the reason for including the analysis></i>
Analysis Purpose	<i><define the purpose of the analysis></i>
Data References (incl. Selection Criteria)	<i><add selection criteria that describes the analysis subset used to derive a result for a display></i>
Documentation	<i><Optional section intended to guide reviewers to external references such as protocol></i>
Programming Statements	<i><add program code used to perform the specific analysis and show how the specific analysis result was created></i>

Statistical Programming (SP) Groups



SP Groups Locations



ADaM Center of Excellence (CoE)



ADaM CoE Team Responsibilities

- Provide support on evaluating new processes, standards, and tools (e.g. ADaM IG 1.1, new releases of Pinnacle 21, etc.)
- New SDTM version impact on ADaM implementation
- Provide review and feedback on updates to impacted documents, execution resources, training materials, etc.
- Provide support for UAT, pilot projects
- Provide support for reviewing ADRG new templates, completion guidelines, Study Data Technical Conformance Guide (TCG)
- Promote consistent implementation of ADaM within & across TAs including use of standards, processes, tools
- Stay current with ADaM related submission requirements
- Serve as a point of Contact for any questions, issues, feedback, suggestions for improvement

Conclusion

- Regulatory submissions are one of the critical milestones in clinical research. High quality submission deliverables is extremely important for regulatory review process
 - Establish collaboration, which is a key to success
 - Successfully achieve timelines and required compliance.
 - Achieve consistent and high-quality submission deliverables across study teams
 - Implement new versions of ADaM standards across study teams with ease
 - Accelerate approval

THANK YOU

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