

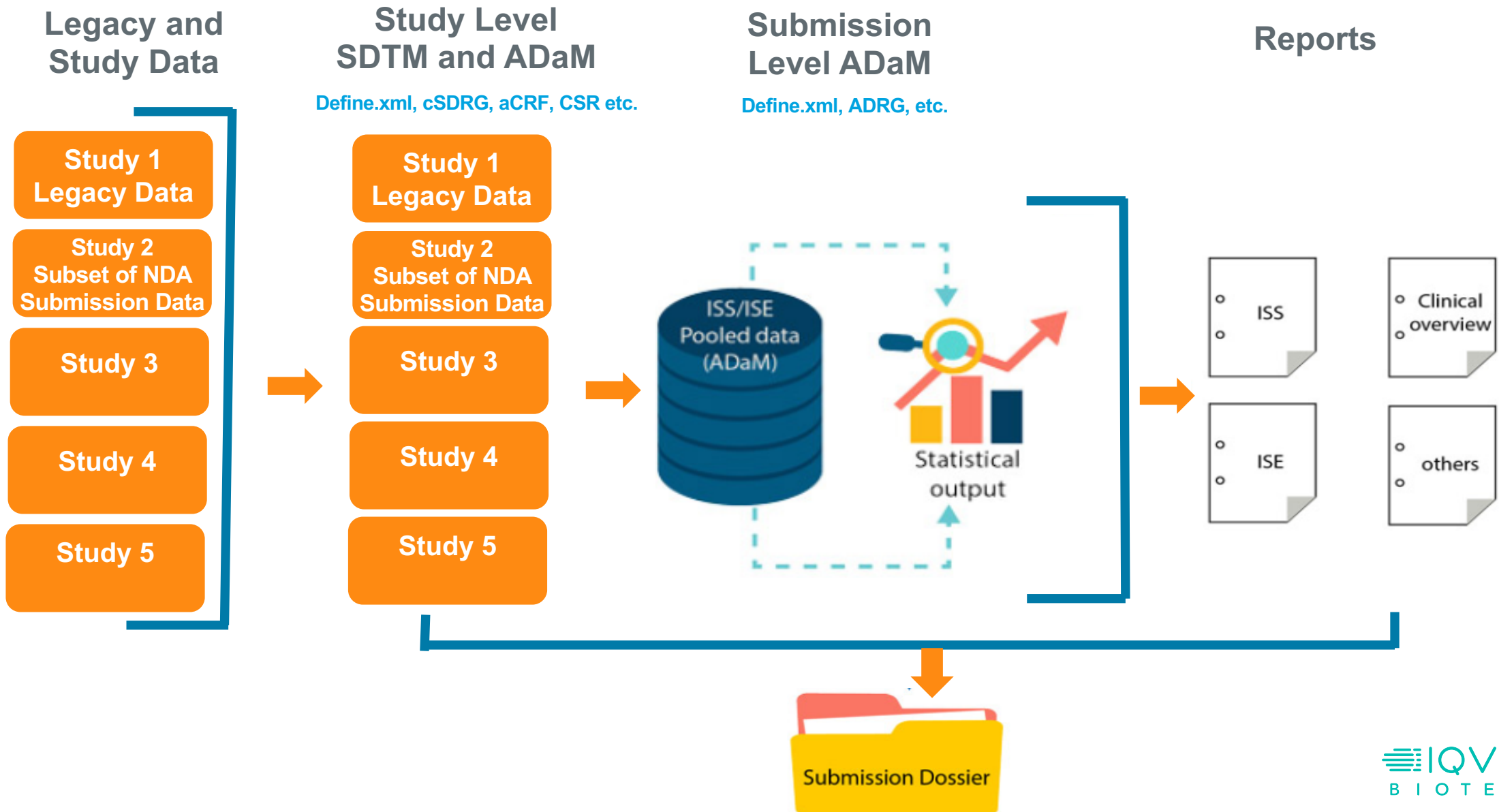
Complexities In Adhering To Data Standards For ISS NDA Submissions

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NDA – ISS FDA Submission – Case Study



FDA-CDISC Guidance Documents for NDA and ISS Submissions

For the NDA and ISS submissions, the following are some key FDA and CDISC Guidance documents that were used as reference documents:

- ❑ *“Guidance for Industry: Providing Regulatory Submissions in Electronic Format – Submissions Under Section 745A(a) of the Federal Food, Drug and Cosmetic Act”*
 - ❑ Most NDAs will need to be submitted electronically in eCTD format.
- ❑ *“Guidance for Industry: Providing Regulatory Submissions in Electronic Format – Standardized Study Data”*.
 - ❑ Studies must utilize specific data standards for the collection, analysis and delivery of clinical and non-clinical trial data and results.
- ❑ *“The Study data Technical Conformance Guide”*
 - ❑ Recommendations, general considerations on how to submit standardized study data using FDA-supported data standards from the FDA Data Standards Catalog.
- ❑ *“The CDISC Submission Metadata Model”*
 - ❑ Guidance document for preparation of data that is to be submitted to the FDA.
 - ❑ By following these principles, any FDA submission can help reviewers accurately interpret the contents of submitted data and work with it more effectively, without sacrificing the scientific objectives of clinical development.



CDISC Standards for NDA and ISS Submissions

Clinical

Plan



Model for Planning

Collect



Model for Data Collection

Organize



Model for Tabulation of
Study Data

Analyze



Analysis Data Model

FDA-CDISC Data Exchange

ODM
XML

Operational Data
Model

Define
XML

Dataset Metadata

Dataset
XML

Operational Data
Model

CTR
XML

Clinical Trial
Registry

RDF

Resource
Description
Framework



CDISC in eTCD Folders

Controlled Terminology



GAP Analysis Ahead Of Submission Data Prep

It is critical to conduct a Gap Analysis to identify the difference in data collection formats and clarify the scope and challenges of the ISS activities. Key tasks as part of the Gap Analysis included:

Itemizing and evaluating files including legacy data to support integration of safety data.

- ❑ **Creating a document inventory (ex. Study documents, FDA and CDISC standards, Company standards and Sponsor requirements)**
- ❑ **Validating sample CRF fields versus source data**
- ❑ **Verifying external data requirements e.g. central labs or local labs**
- ❑ **Comparing protocol amendments/versions against CRF versions**

In this initial stage, it is necessary to assess the status of the data which had already, or partially been migrated into SDTM and quantified any gaps. It is an opportunity to do a “first-look” of the raw datasets and compare the aCRF against the raw datasets from the legacy and other studies. As part of this analysis, it is important to look at the status of medical coding for conmeds and AEs and to bring coding up to date with the latest version of MedDRA.

Complexities In Preparing Submission Data

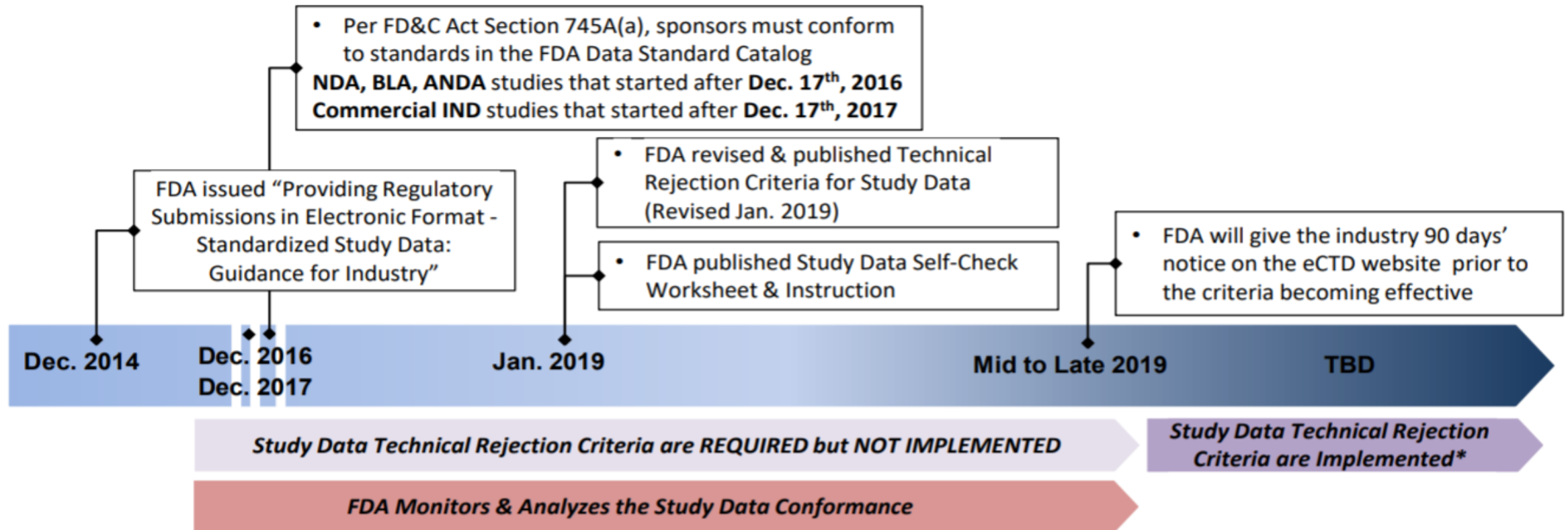
- Every study submission is unique and needs careful planning to avoid costly delays.
- Preparing legacy data for submission must be done carefully to retain the scientific integrity of the data.
- Develop a sound plan on how to deal with legacy data and get approval from the agencies ahead of time.
- During the preparation of legacy data for submission it is very likely that discrepancies will be found. Plan enough time and resources for investigation and resolution.
- Perform additional validation steps against the original study results based on a risk assessment if legacy data is retrospectively mapped.
- Include sufficient documentation with submission data to make the preparation process, findings, discrepancies, and special cases transparent.

FDA Implementation Timelines

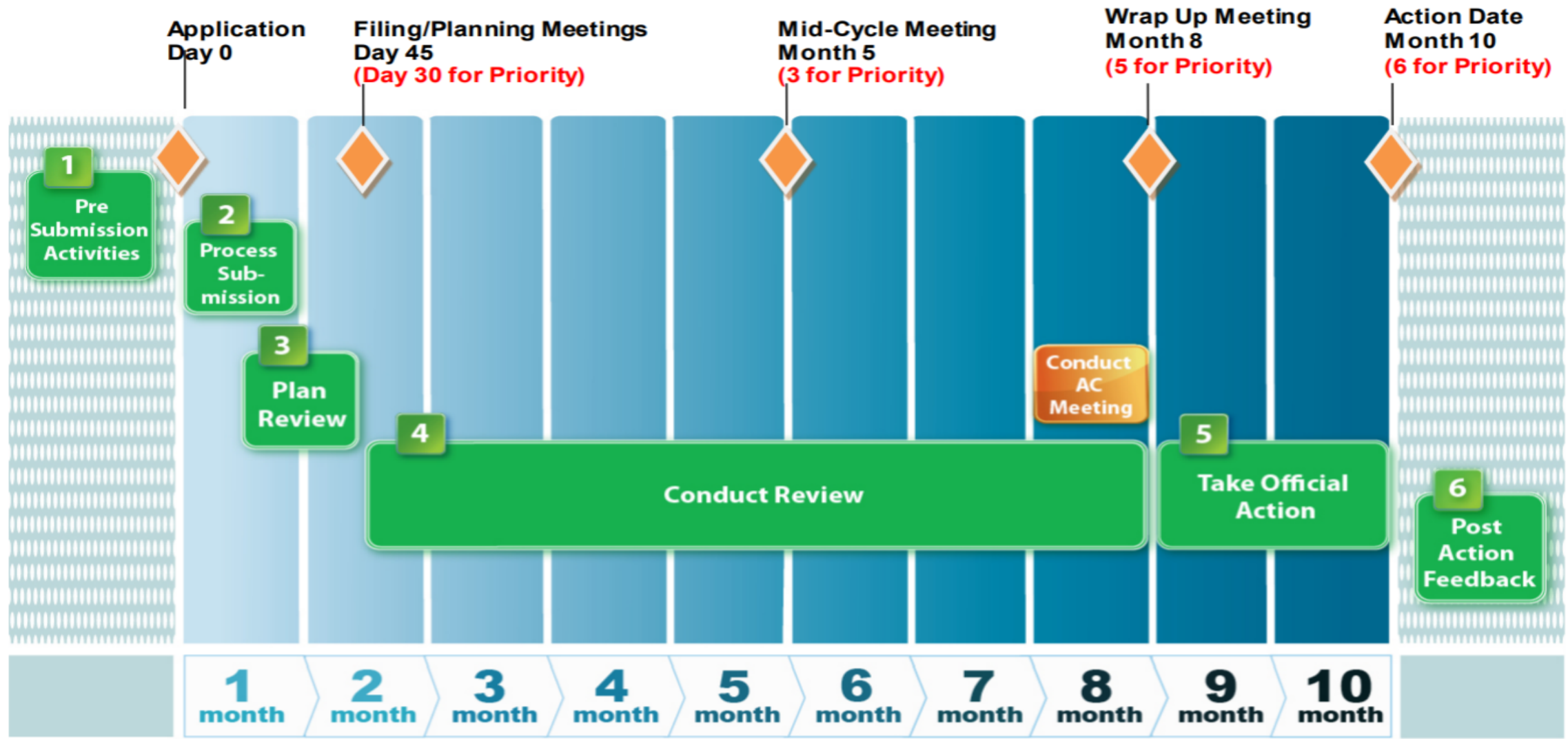


Implementation Timeline

FDA published Revised Study Data Technical Rejection Criteria (Revised Jan. 2019) and Study Data Self-Check Worksheet to assist sponsors with the TRC Conformance



Overview of NDA Review Process – Case Study



Challenges Faced in NDA-ISS Submission Process

- ❑ Sponsors tend to use external vendors to provide analytical models and forecasting projections of the study data that often results in re-work of analyses, and reruns of SDTMs/ADAMs and TLFs.
- ❑ With a myriad of external reviewers re-checking/re-validating the efforts of the partner CRO, it resulted in low morale and early panic about study deliverables and unrealistic timelines.
- ❑ Reconciliation of 5 ISS datasets including gathering data from an external vendor database for the study was a major challenge especially since the external databases were neither RAVE nor INFORM or any of the common databases used in CROs.
- ❑ Getting all the MedDRA coding versions in sync especially since the legacy data used a different version of MedDRA was a notable challenge during NDA-ISS data preparation.

Some Solutions for NDA-ISS Submission Challenges

- ❑ Plan well ahead with an NDA-ISS submission. Set up a core team especially for an NDA-ISS submission that will stay during the entire life cycle of the NDA-ISS submission process to provide continuity. Avoid frequent turnover in the core team.
- ❑ Have a good and feasible ISS integration strategy that would work for the entire life cycle of the NDA-ISS process.
- ❑ Avoid committing to unreasonable deliverables during the life cycle of the NDA-ISS project. Make sure all the teams within the company that are associated with an NDA-ISS project are aware of the company processes.
- ❑ Perform a Risk Analysis ahead of any non-deliverable situation during the course of the submission process.
- ❑ Keep the study teams constantly updated and motivated during the entire life cycle of the NDA-ISS submission process.

Q&A

