Statistical Analysis Plan and Clinical Study Report

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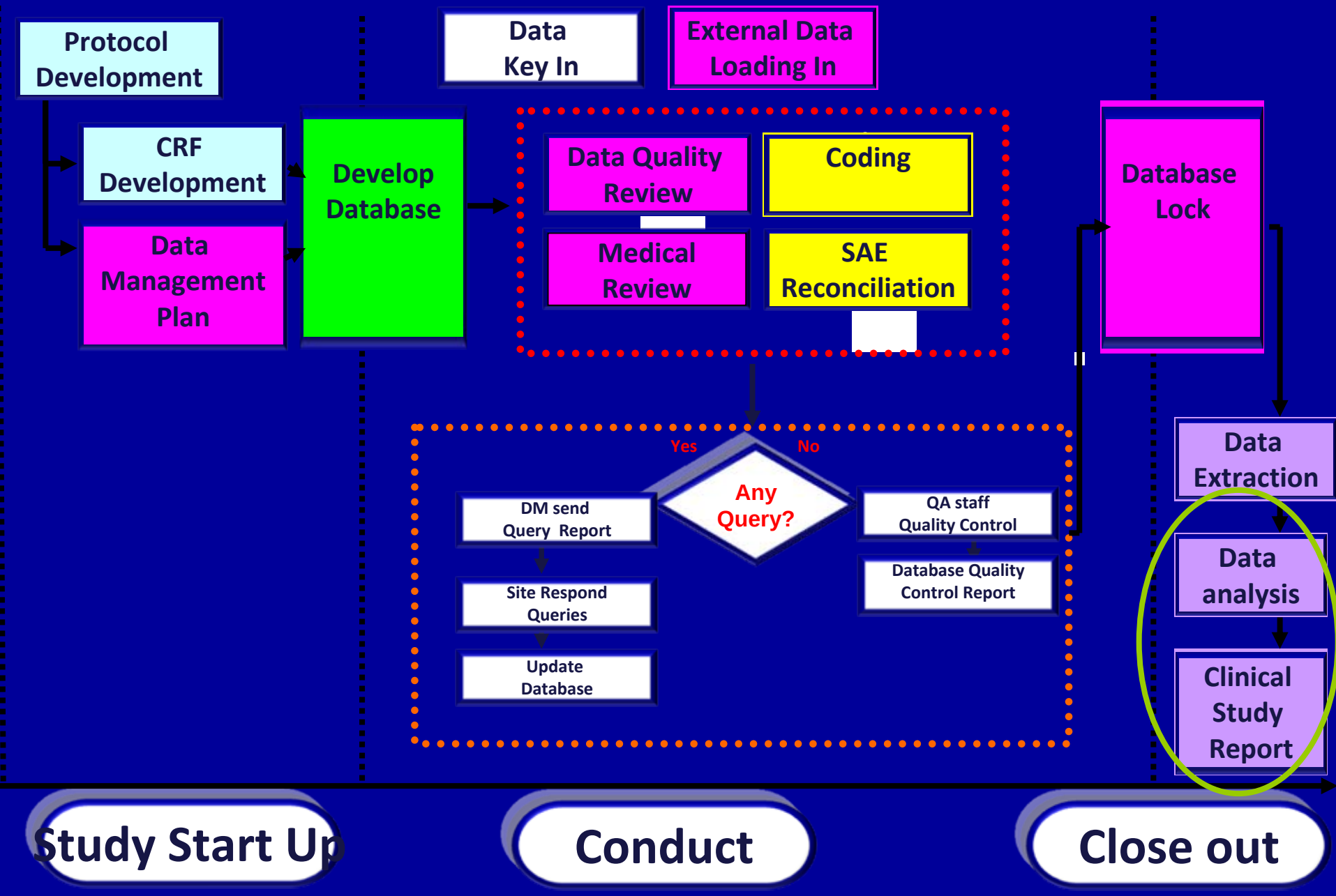
Before Presentation…

- This slide deck is based on Jain Chung's presentation for the 1st CDM training course in 2008.

DM Flow


Protocol Development
CRF Development
Data Management Plan
Develop Database
Data Key In
External Data Loading In
Data Quality Review
Coding
Medical Review
SAE Reconciliation
Database Lock
Yes
No
Any Query?
DM send Query Report
Site Respond Queries
Update Database
QA staff Quality Control
Database Quality Control Report
Data Extraction
Data analysis
Clinical Study Report
Study Start Up
Conduct
Close out

Outline

- **Introduction of Statistical Analysis Plan**
- **Introduction of CSR contents**
- **Final TLFs and Review CSR**

ICH E9 Statistical Principles

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

STATISTICAL PRINCIPLES FOR CLINICAL TRIALS
E9

Current *Step 4* version

dated 5 February 1998

ICH E3 Clinical Study Reports

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

STRUCTURE AND CONTENT OF CLINICAL STUDY REPORTS
E3

Current *Step 4* version

dated 30 November 1995

Introduction of Statistical Analysis Plan (SAP)

- What is SAP?
- Why need a SAP?
- When write a SAP?
- What are included in the content?
- Who write the SAP?

Statistical Analysis Plan is ... (ICH E9)

- a document that contains a more technical and detailed elaboration of the principal features of the analysis described in **the** protocol, and includes detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

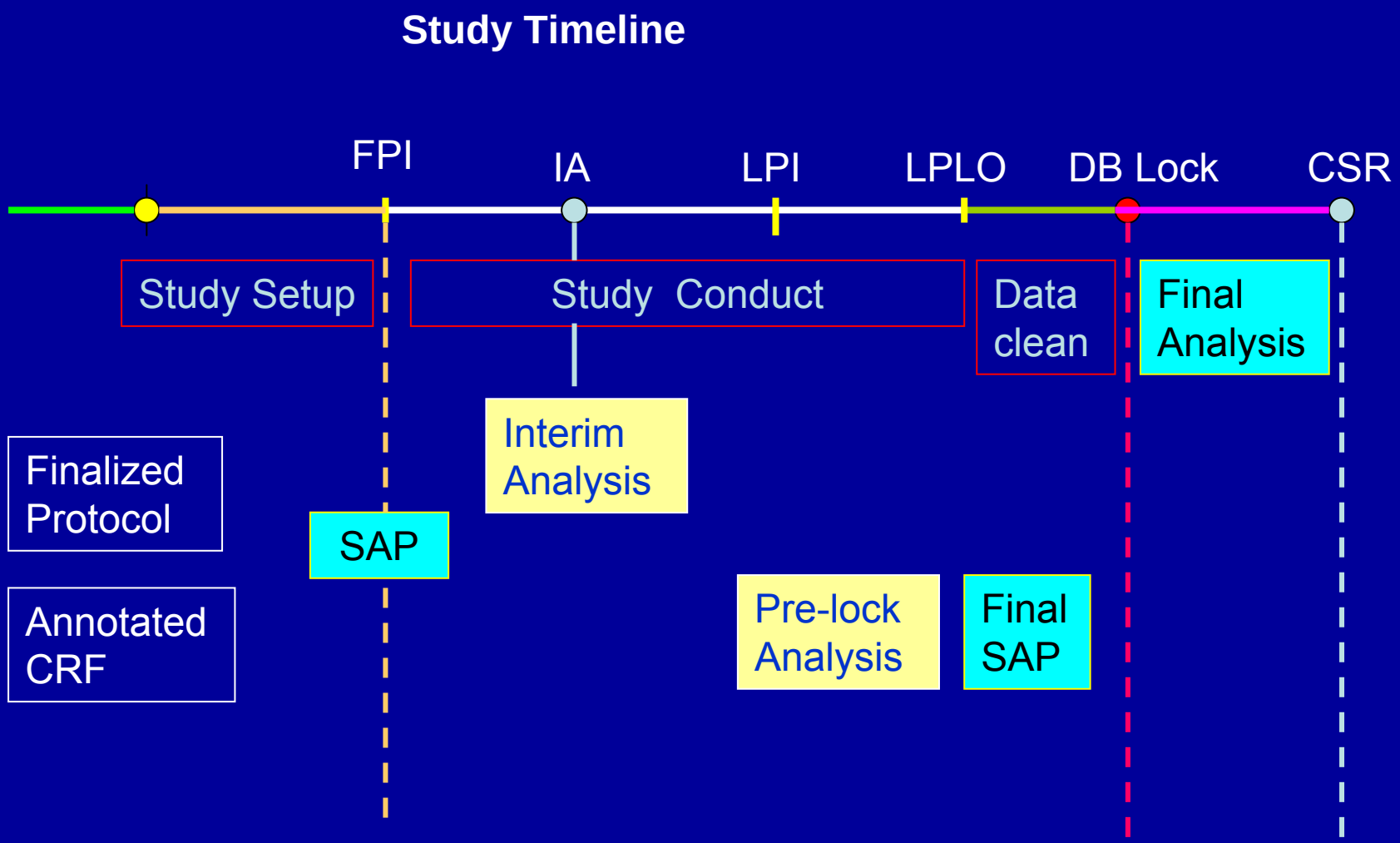
What is SAP?

- Also called Data Analysis Plan (DAP)
- An essential document for biometrics activities
- A guidance for a final clinical study report
- A guidance for analysis program development

Why Need a SAP?

- Provide details of data handling rules and statistical analysis methods used for efficacy and safety reporting
- Identify all tables, listings, and figures to be used for the reports
- Document detail deviations from the protocol
- Facilitate SAS program development
- Fulfill Health Authority requirements

When write a SAP?



What Are Included in the Content?

1. General information
2. Evaluations Perform. Before DB closure
3. Analysis Populations
4. Patient Disposition
5. Baseline Characteristics
6. Efficacy Analysis
7. PK/PD Analysis *(if applicable)*
8. Safety Analysis

…

References

Appendices

1. General Information

- **Protocol number**
- **Title**
- **Study Objectives**
- **Study design**
- **Sample size and randomization algorithm**

2. Evaluations Performed Analysis before Database Closure

- Evaluation of possibility of introduction of biases
  - DSMB activities
  - Interim analysis
  - Procedures used for program development and validation
- Exact procedure for handling blinding
- Early/late pre-analysis reviews of blinded data

2.2 DSMB

- Composition, purpose and responsibility
- Membership (internal, external or mixed)
- Project team members involved
- Performed by third party outside Biometrics: Reporting objects should not be described in SAP but in DSMB Charter

2.3 Interim Analysis

Interim analysis performed by Biometrics have to be included the followings in the SAP

- **The purpose**
- **Timing of analysis**
- **Un-blinding procedure/integrity**
- **Individual patient results or patient summaries, display of treatment arms (yes/no)**
- **Distribution of results**

3. Analysis Populations

Definition of patient populations including details of the criteria used for classification

- **ITT (FAS)**
- **PP**
- **Safety**
- **Others**

4. Patient Disposition

Counting the number of patients

- **Included in the study**
- **Randomized**
- **Treated**
- **In ITT and PP**
- **In Safety Analysis**
- **Prematurely withdrawn**

5. Baseline Characteristics

Assess the comparability among treatment groups

- **Demographics**
- **Baseline characteristics**
- **Previous disease/medications**
- **Concomitant medication/procedures**

6. Efficacy Analysis

Sufficient level of details to enable a third party to repeat the analysis

- **Definition of time windows**
- **Definition of baseline values**
- **Descriptions of derivation algorithms**
- **Definitions of primary, secondary, tertiary endpoints**
- **Statistical methods and models used**
- **Detail information of handling multiplicity and missing data**
- **Sensitivity analysis (e.g. different data handling rules)**
- **Robustness analysis (e.g. different analysis populations)**
- **Subgroup analyses**
- **Additional Exploratory Analysis**

7. PK/PD Analysis if applicable

- PK/PD analysis datasets
- The data presentations for the PK profiles and derived PK parameters that produced for the CSR

  {This should be done in collaboration with Clinical Pharmacologist}
- Modeling, derivation and simulation performed by *Clinical* Pharmacologist if applicable

8. Safety Analysis

- **Exposure to study medication**
- **Adverse Events (specifies special adverse events)**
  - AE by body system and preferred terms
  - Serious AEs
  - AE by intensity and by relationship
- **Withdrawals**
- **Death**
- **Laboratory Parameters**
- **Special Areas of Interest (anything additional)**
- **Vital Signs**
- **ECGs**

May also be Included in SAP…

- Immunogenicity analyses (if applicable)
- Follow up analysis
- Changes from protocol DAS and additions after Database closure
- Separate (sub-)sections for: statistical methods, multiplicity adjustments, ground rules and data Handling conventions

References

- List all references used in the SAP

Appendices

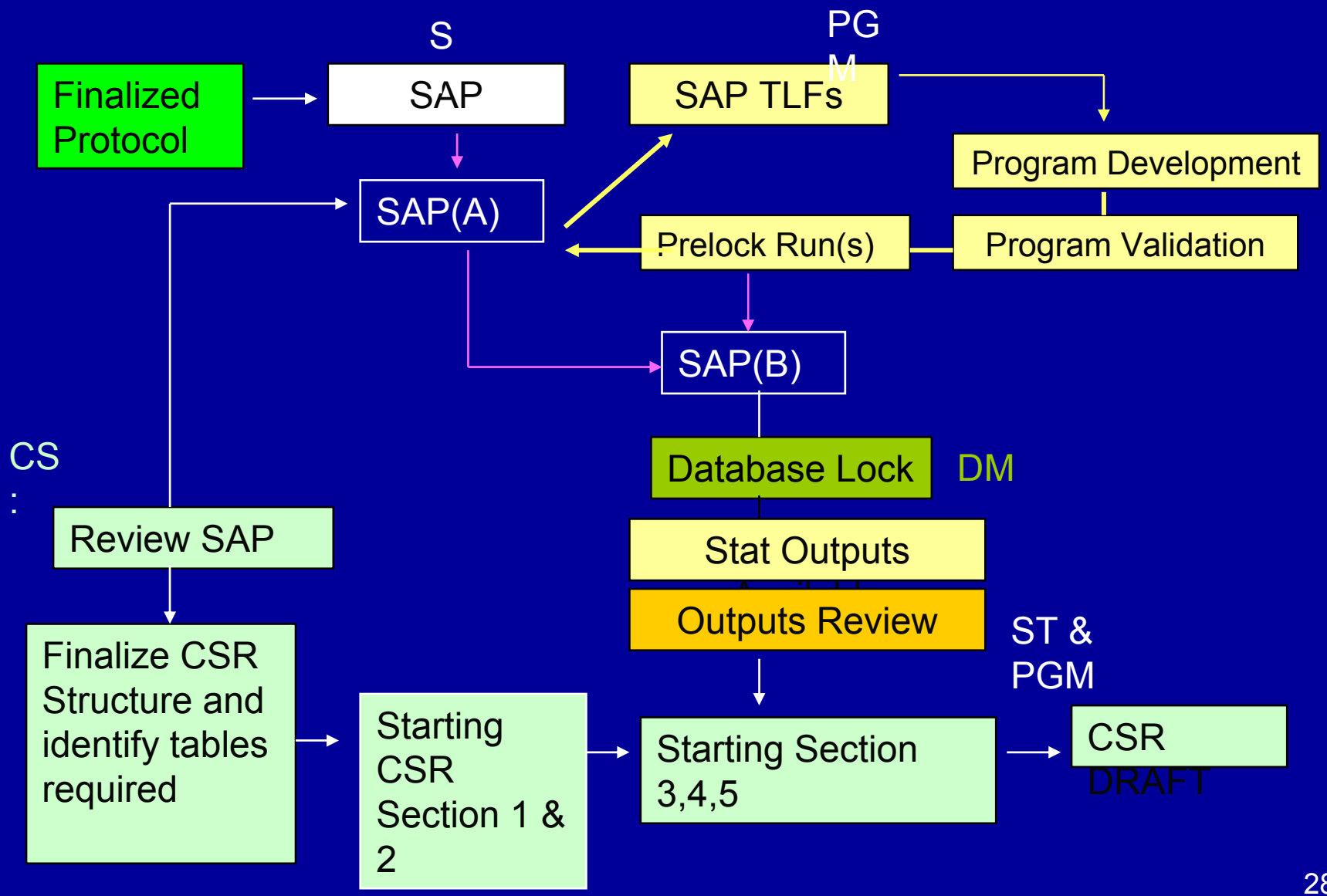
- List of appendices attached to the SAP
- Appendices may include an example of a questionnaire, an example of statistical output, study flow chart, key derivation or definitions, list of TLFs, etc.

Who write the SAP?

- Study Statistician

Introduction of CSR Contents

Process for Development Clinical Study Report



Sample of CSR Report Body

In the format of the Journal-Style scientific paper

1. Background, Rationale and Objectives
2. Materials And Methods
3. Results
   - 3.1 Study Population
   - 3.2 Efficacy Results
   - 3.3 Pharmacodynamic, Pharmacokinetic and PK/PD Modeling
   - 3.4 Safety Analysis
4. Discussion
5. Conclusion
6. References

Appendices

Sample of CSR Report Body

In the format of ICH E3 "Structure and Content of Clinical Study Reports"

1. Title page
2. Synopsis
3. Table of contents
4. List of abbreviations
5. Ethics
6. Investigators and study administrative structure
7. Introduction
8. Study objectives
9. Investigational plan
10. Study patients
11. Efficacy evaluation
12. Safety evaluation
13. Discussion and overall conclusions
14. Tables, figures and graphs referred to but not included in the text
15. Reference list
16. Appendices

CSR Section 3 - Results

3.1 Study Population

- 3.1.1 Disposition of Patients
- 3.1.2 Patients Withdrawn Prematurely from treatment
- 3.1.3 Overall of Analysis Populations
- 3.1.4 Protocol Violations
- 3.15 Demographic Data and Baseline Characteristics
- 3.1.6 Previous Concomitant Medications and Diseases

CSR Section 3 - Results

3.2 Efficacy Results

3.2.1 Primary Efficacy Parameter

3.2.2 Secondary Efficacy Parameter (s)

3.1.3 Subgroup and Exploratory Analyses

3.3 Pharmacodynamic, Pharmacokinetic and PK/PD Modeling

CSR Section 3- Results

3.4 Safety Analysis

- 3.4.1 Extent of Exposure to Trial Medication
- 3.4.2 Overview of Safety
- 3.4.3 Adverse Events

- 3.4.3.1 Overview Adverse Events
- 3.4.3.2 Deaths
- 3.4.3.3 Serious Adverse Events
- 3.4.3.4 Adverse Events and Laboratory abnormalities Leading to Withdrawal from treatment
- 3.4.3.5 Dose Modifications for Safety Reasons

CSR Section 3 - Results

3.4.4 Laboratory Parameters

3.4.4.1 Mean (or Median) Change from Baseline

3.4.4.2 Shift from Baseline

3.4.5 Vital Signs

3.4.6 ECGs

Other CSR Sections: 4, 5, and 6

4. Discussion
5. Conclusion
6. References

   Appendices

Review CSR, final TLFs

- Validation
- Consistency
- Interpretations
- Discussions

BACK-UP SLIDES

CSR Section 1: Background, Rationale and Objectives

1.1 Background
1.2 Rationale
1.3 Objective

CSR Section 2 - Materials and Methods

2.1 Overall Study Design

2.1.1 Protocol Amendments

2.2 Study Population

2.2.1 Overview

2.2.2 Inclusion Criteria

2.2.3 Exclusion Criteria

2.2.4 Criteria for Withdrawal from Treatment or Study and Replacement Policy

2.2.5 Concomitant Medication, Treatments and Procedures

2.3 Compliance with Good Clinical Practice

2.3.1 Ethics

2.3.2 Audits

2.3.3 Data Quality Assurance

2.4 Trial Medication

2.4.1 Rationale for Dosage Selection

2.4.2 Formulation and Packaging

2.4.3 Assignment to Treatment Group/Sequence

2.4.4 Blinding

2.4.5 Drug Administration

2.4.6 Dose Modification

2.4.7 Dose Accountability and Compliance

ICH E3 Structure and Content of Clinical Study Reports

1. Title page
2. Synopsis
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** Details for Sections 9 – 12 on next slides*

ICH E3 Structure and Content of Clinical Study Reports (cont.)

9. Investigational plan

9.1 Overall study design and plan description

9.2 Discussion of study design, including the choice of control groups

9.3 Selection of study population

- 9.3.1 Inclusion Criteria
- 9.3.2 Exclusion Criteria
- 9.3.3 Removal of Patients from Therapy or Assessment

9.4 Treatments

- 9.4.1 Treatments Administered
- 9.4.2 Identity of Investigational Product(s)
- 9.4.3 Method of Assigning Patients to Treatment Groups
- 9.4.4 Selection of Doses in the Study

9.4 Treatments (cont.)

- 9.4.5 Selection and Timing of Dose for each Patient
- 9.4.6 Blinding
- 9.4.7 Prior and Concomitant Therapy
- 9.4.8 Treatment Compliance

9.5 Efficacy and safety variables

- 9.5.1 Efficacy and Safety Measurements Assessed and Flow Chart
- 9.5.2 Appropriateness of Measurements
- 9.5.3 Primary Efficacy Variable(s)
- 9.5.4 Drug Concentration Measurements

9.6 Data quality assurance

9.7 Statistical methods planned in the protocol & determination of sample size

9.8 Changes in the conduct of the study or planned analyses

ICH E3 Structure and Content of Clinical Study Reports (cont.)

10 Study patients

10.1 Disposition of patients

10.2 Protocol deviations

11. Efficacy evaluation

11.1 Data sets analyzed

11.2 Demographic and other baseline characteristics

11.3 Measurements of treatment compliance

11.4 Efficacy results and tabulations of individual patient data

12. Safety evaluation

12.1 Extent of exposure

12.2 Adverse events (AEs)

12.3 Deaths, other SAEs, and other significant adverse events

12.4 Clinical laboratory evaluation

12.5 Vital signs, physical findings and other observations related to safety

12.6 Safety conclusions

References

- ICH Guidelines www.ich.org
  - E9 Statistical Principles for Clinical Trials
  - E3 Structure and Content of Clinical Study Reports

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