Statistical Analysis Plan and Clinical Study Report

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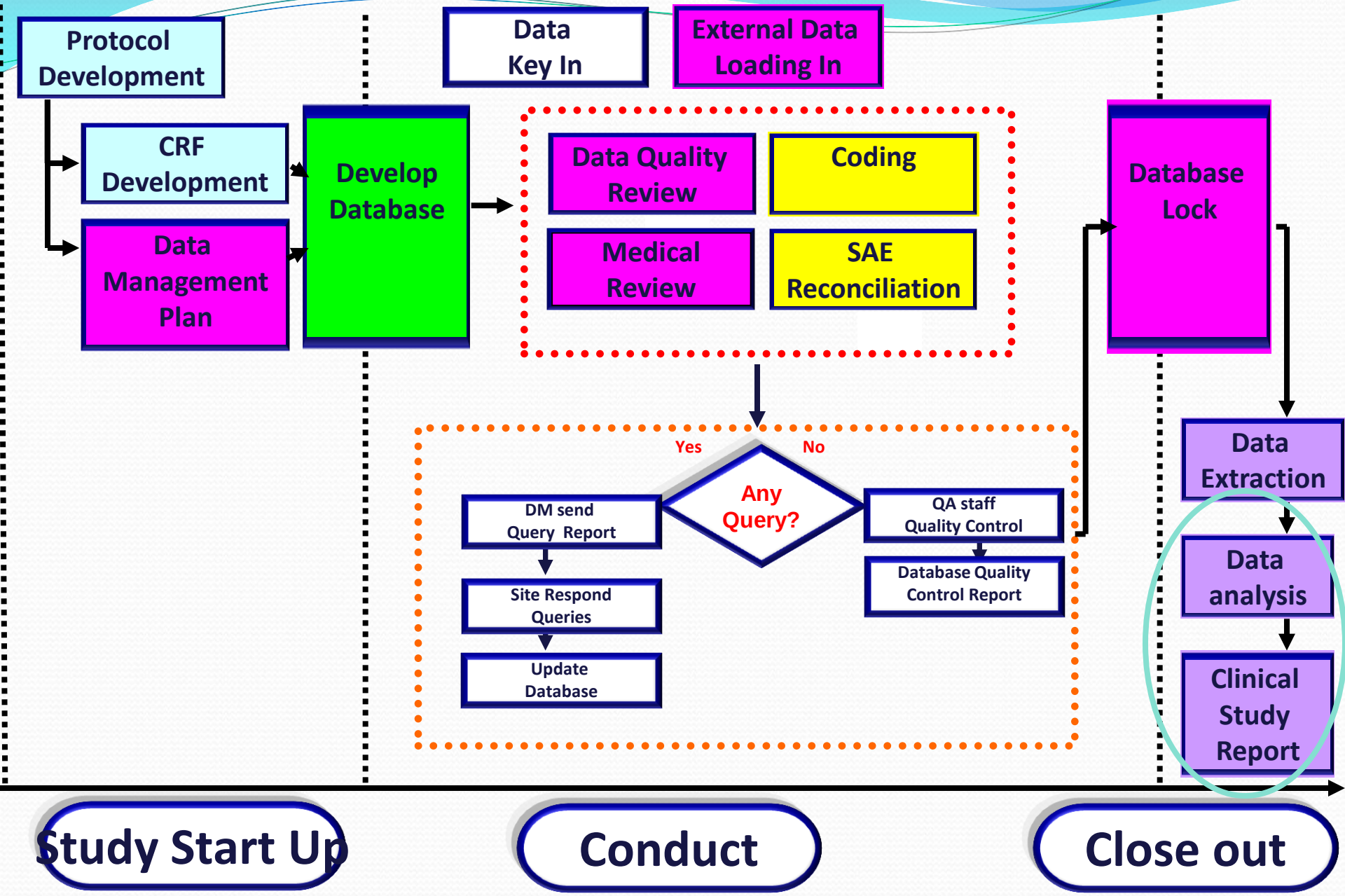
Data Management Flow



Outline

- Introduction to Statistical Analysis Plan
- Introduction to CSR contents
- Final Tables Listings and Figures (TLFs)and Review CSR

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

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.

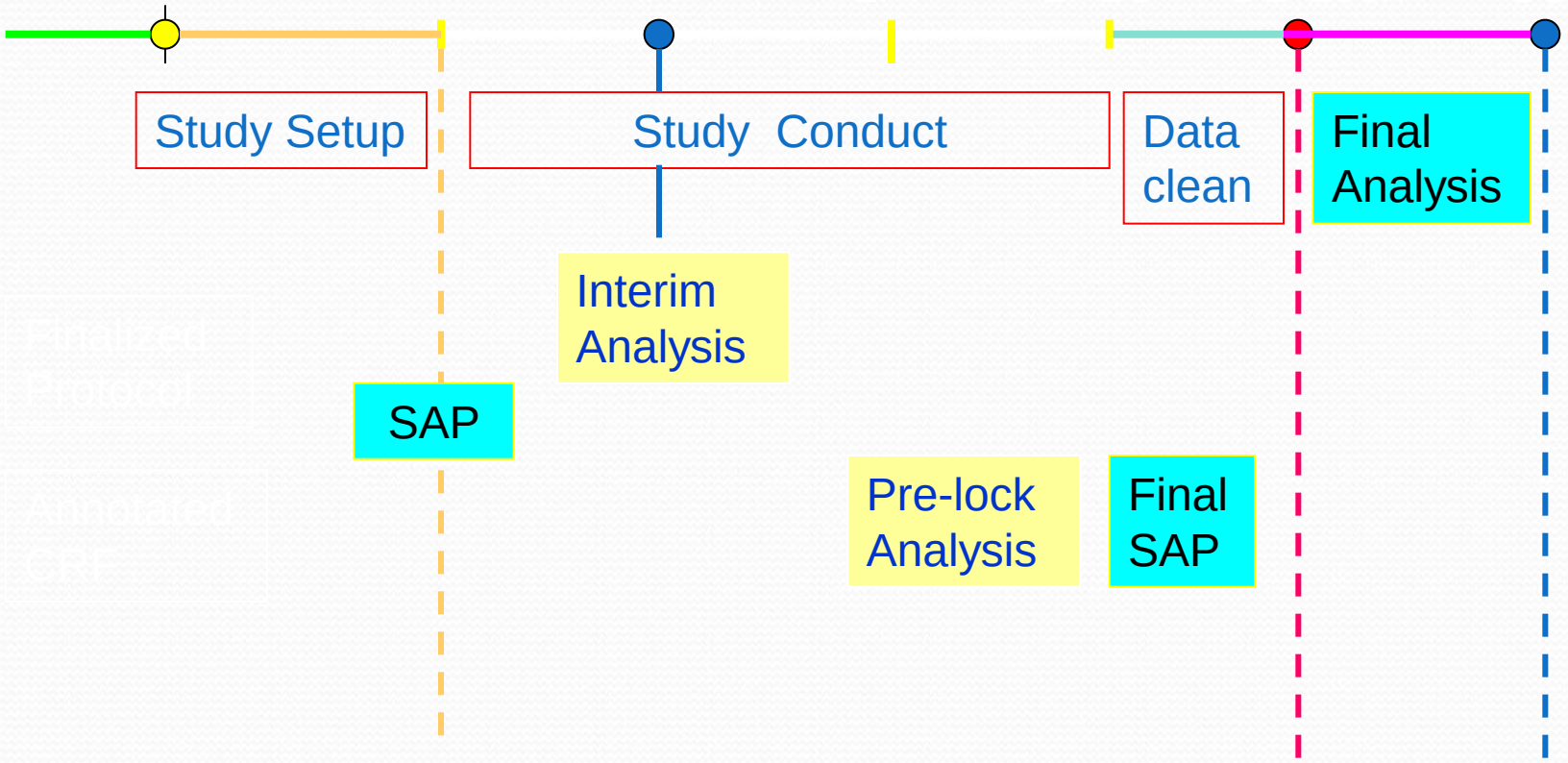
What is SAP?

- 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

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

Clinical Study Report (CSR)

CSR

- A CSR is a scientific document addressing efficacy and safety, not a sales or marketing tool
- However, key messages are important study findings that are repeated throughout the marketing application.
- In the CSR, key messages are found in the synopsis at the beginning and are reiterated in the body of the document as topic sentences, in summaries of sections or subsections, and in the conclusions

CSR

- A CSR is a descriptive account of a single clinical trial accompanied by tables, listings, and figures (TLFs) displaying all study data and results.

- The content of a CSR is similar to that of a peer reviewed manuscript. The CSR includes summary sections, appendices, and many details, but the meat of the document is comprised of sections already familiar : introduction and background, experimental methods, description of study subjects, efficacy results, safety results, and conclusions.

Documents to read before writing a CSR

- Disease: what is it?
- Protocol
- IB
- Study Manual
- SAP
- The tables, listings, and figures (TLFs)
- DSMB minutes and recommendations

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

Introductory Sections

- Can be derived from the protocol sections
- Briefly identify the study population and objectives
- Summarize the protocol or the protocol synopsis.

Methods

- The protocol and SAP already describe methods, so paste the methods from those documents into the CSR and put them in past tense, simplifying to exclude unnecessary details.
- Explain the randomization plan in full
- Describe who is blinded and how blinding was maintained.
- Discuss breaches of protocol that threaten blinding and any premature unblinding, if any.

Study Subjects

- Describe the study population and disposition of subjects in detail.
- Report screening failures, subjecst who have discontinued or withdrawn due to adverse events, etc
- Report these events by using a table or figure providing reason for such events by vaccine group
- Assess subject compliance with study treatment procedures, if took all vaccine doses

Study Population

- At least two populations ar
  protocol and SAP of vacci
- The intention to treat po
  of all randomized subject
  dose of the study vaccine(
- The per protocol population
  randomized subjects who recei oses
  of vaccine and completed the stu cording protocol
- In a perfect clinical trial with 100% compliance ITT and PP would contain the same subjects

Do you remember about compliance and what can be the effect of poor compliance?

Study Population

- In real world ITT # PP
- ITT is the safety population, demographic characteristics are analiyzed in the ITT
- PP is the efficacy population, but ITT is also analyzed as secondary analysis for efficacy
- If clinical study compliance has been poor analysis of ITT and PP on baseline and demographics may be necessary to show whether there is any difference between ITT and PP

Study Population

Clearly state which study population is described in text sections and in-text tables and figures within the CSR.

Immunogenicity/Efficacy

- Discuss with study statistician and other study team on the results
- Describe first the primary outcome clearly and supported by tables
- Describe then the secondary outcome in decrasing order of importance supported by tables, figures, RCDC etc

Safety

- Safety results usually include clinical laboratory values, adverse events, vital signs, medical history, and examination findings
- AEs have to be described in detail and according their relationship to study vaccine(s) with p-values
- SAEs one by one with a detailed narrative and if sufficient tabulated with p-values (AEI) by age group, organ system class etc
- It is never correct to mislead or fail to report important information, but placing undesirable study results into context is acceptable

Safety

- Carefully study the adverse events, then dig through other data to see whether explanatory factors are present for subjects experiencing concerning adverse events.

- Use the medical history and physical examination, including those performed at baseline, eligibility violations,compliance data, concomitant medications, vital signs, clinical laboratory values, and anyother relevant data you may identify

- Present all data that support a relationship between an adverse event and a factor other than the study product.

Conclusions

- Summarize important safety and efficacy findings.
- Study conclusions should mention the study primary and secondary objectives
- State whether those were achieved, and reiterate the key messages

Final tips

- Be flexible in following the E3table of contents, but maintain its structure and chronology.
- Final grammatical error checking is essential, and ideally should be performed by someone other than the primary writer. Verify every fact in the text and in-text tables and figures.
- Understand how a CSR fits into the larger product approval process. A marketing application includes multiple CSRs and other summary documents.

Final Advice

- CSR is a co-authored document
- None can write a CSR alone
- If you are the leading author, accept others views and opinions
- Stylistic disagreements about content and composition are rarely critical, so unless you believe an inclusion or omission is scientifically dishonest, remain flexible.

References

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