# Clinical Study Reports:

## Variation Across the Study Types and Reporting Formats

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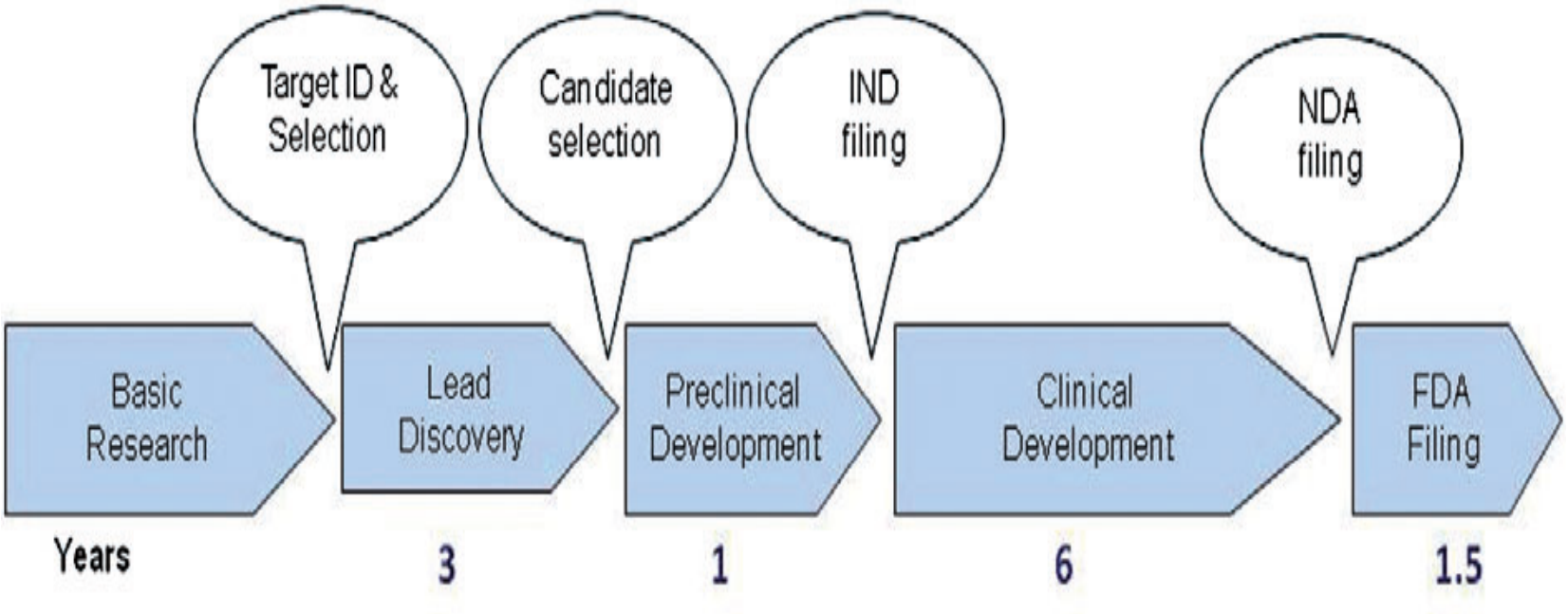
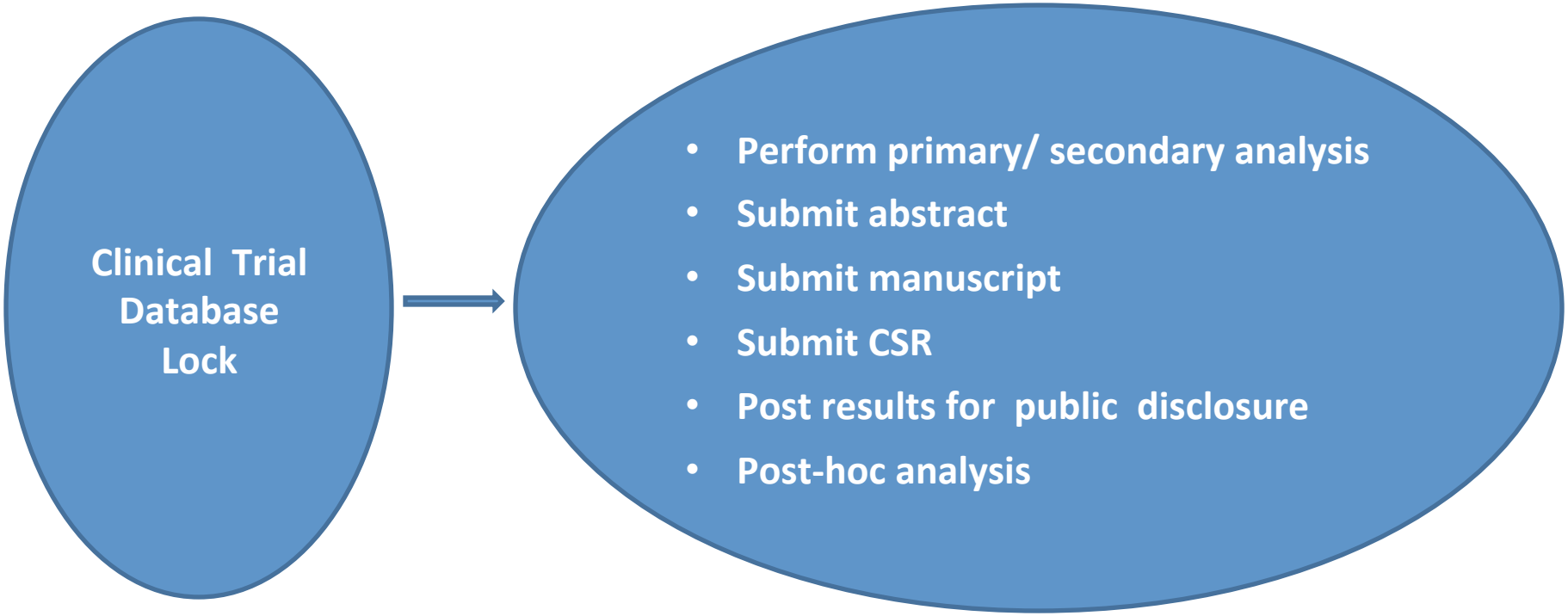
# Overview of Drug Development




Estimates for development of a new drug are now in the order of $0.5 - 2 billion

# Data Analysis/Publication Phase

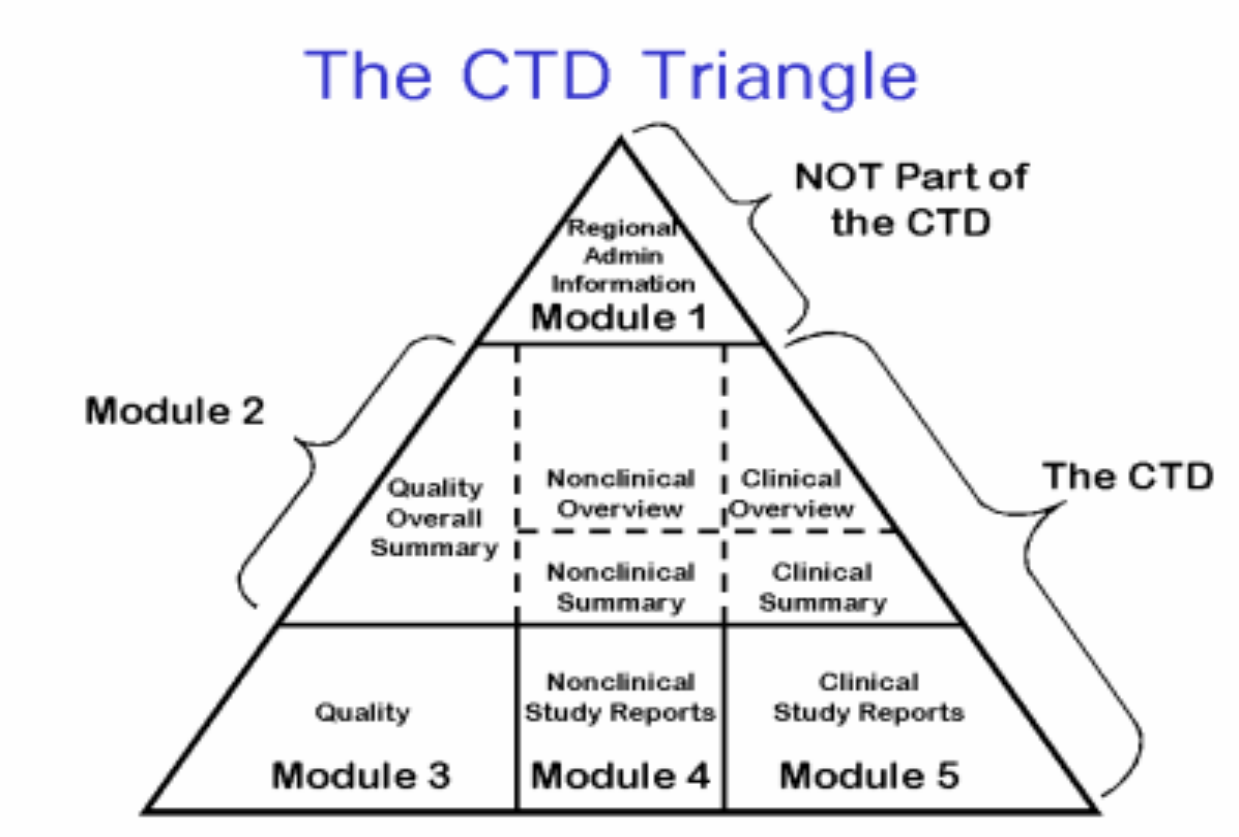


# What is CSR?

A written description of a trial/study of any therapeutic, prophylactic, or diagnostic agent conducted in human subjects, in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report.

The CSR should be written in a format that is acceptable to all regulatory authorities.

# Common Technical Document (CTD) Modules




**CTD: Common modular format for Drug Registration applications worldwide**

# Location of CSR

The particular location of a CSR within the CTD (Module 5) is determined by the primary objective of the study: eg, efficacy and safety, PK, or PD

5.3 Clinical Study Reports

5.3.1 Reports of Biopharmaceutical Studies

5.3.2 Reports of Studies Pertinent to PK using Human Biomaterials

5.3.3 Reports of Human PK Studies

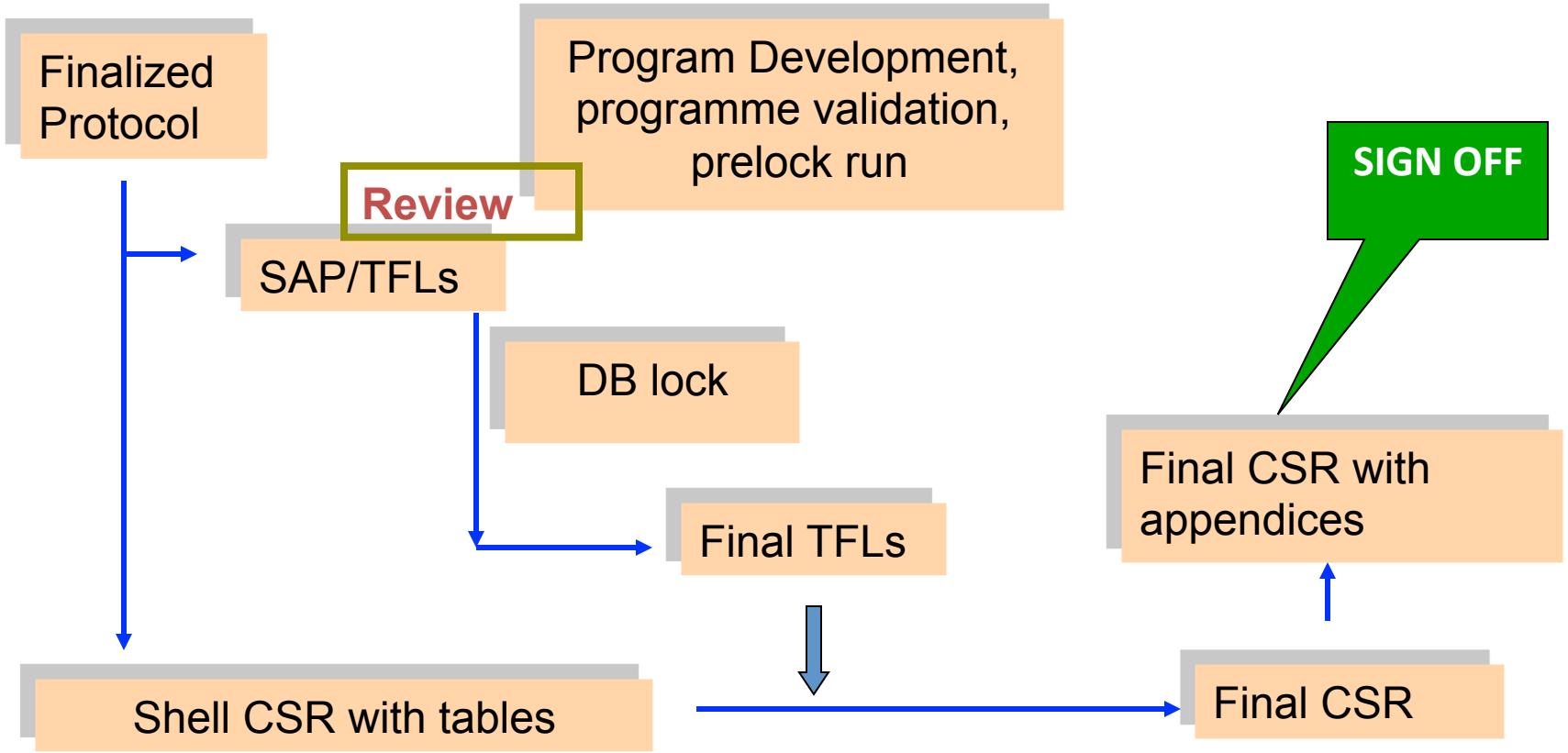
5.3.4 Reports of Human PD Studies

5.3.5 Reports of Efficacy and Safety Studies

5.3.6 Reports of Post-Marketing Experience

5.3.7 Case Report Forms and Individual Patient Listings

# Process for Development CSR



# Regulatory Guidance on CSR

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

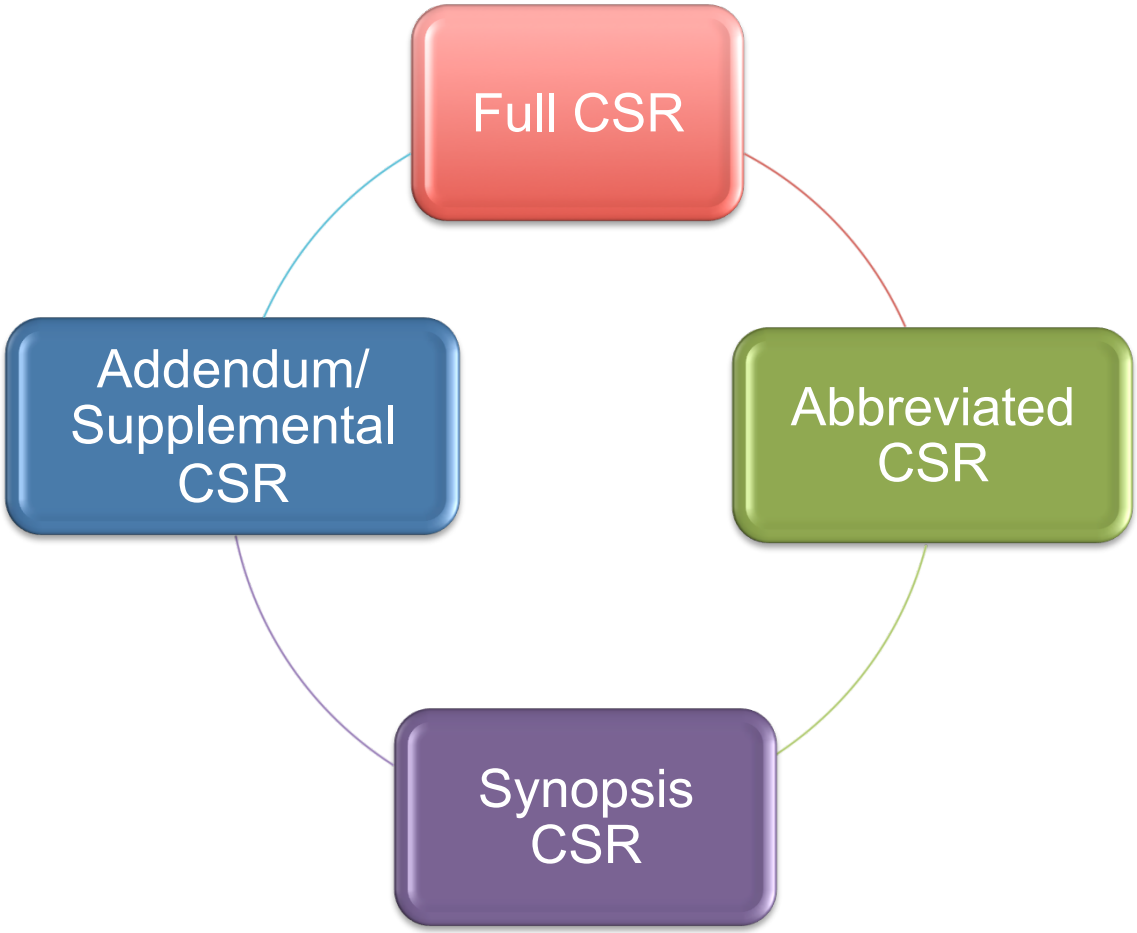
*This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.*

**Guidance for Industry**

**Submission of Abbreviated Reports and Synopses in Support of Marketing Applications**

- ICH E3 allows for "abbreviated reports using summarized data or with some sections deleted"
- FDA guidance outlines content for "Abbreviated" and "Synopsis" CSRs
- "Supplemental CSR" not defined in regulatory guidance

# CSR Type and Format



# Global regulatory requirements for reporting results

- Primary outcomes for clinical studies should be reported to the applicable regulatory authorities within 1 year of the time point defined in the protocol as the Primary Completion date.
- This requirement applies to all phase 1 to 4 non-pediatric studies
- The requirement can be satisfied by submission of a CSR, CSR synopsis, or similar summary of study results and conclusions

# Global regulatory requirements for reporting results

FDA is more driven by end of trial date whereas EU by primary completion date for analyses of efficacy. Primary analysis CSR is required 1 year from primary completion date

Health Canada: Requires a notification for a completed study, however, no supporting information is required with the notification, i.e. a final study report is not required.

SFDA China: After completion of the Multi-Regional Clinical Trials, the sponsor must submit the global study report, the statistical analysis report, the databases, and relevant supporting data, as well as the comparative and trending analysis of the data from Asian and Chinese subgroups against other subgroups.

# Submission of Pediatric Study Reports

EU requirement:

- CSR synopsis must be submitted to EMA and each competent authority within 6 months after study completion or termination (ie, last subject last visit)

- If it is not possible to submit the CSR synopsis within 6 months, a scientific justification and the study results need to be submitted to the EMA and each competent authority within 12 months after study completion or termination

# Full CSR

All clinical and human pharmacology investigations that contribute to the evaluation of effectiveness for the proposed indication, or that otherwise support information included in labeling

- Studies providing the basis for dose recommendations
- (e.g., dose comparison studies)
- Controlled studies identified by the applicant as contributing directly to substantial evidence of effectiveness.
- Controlled studies that support an intended comparative claim

- Controlled studies considered supportive of effectiveness (e.g., studies believed to show a favorable trend, possible effect in a subgroup)
- All studies from limited development programs (programs with < 6 clinical trials)
- Any study included in a Paediatric Investigation Plan (PIP) as a binding measure

# Synopses CSR

Studies that are not relevant to the evaluation of product effectiveness or clinical pharmacology, but that provide information the reviewer needs to evaluate the safety data from the study

- Studies of unrelated indications
- Incomplete studies or Discontinued studies
- Uncontrolled studies not specifically identified as needing abbreviated or
- Full study reports

- Studies evaluating dosing regimens not intended for marketing
- Early general phase-1 safety-tolerance studies not supporting labeling statements
- BA/BE studies not assessing performance of material used in clinical trials relative to dosage forms intended for marketing

# Abbreviated CSR

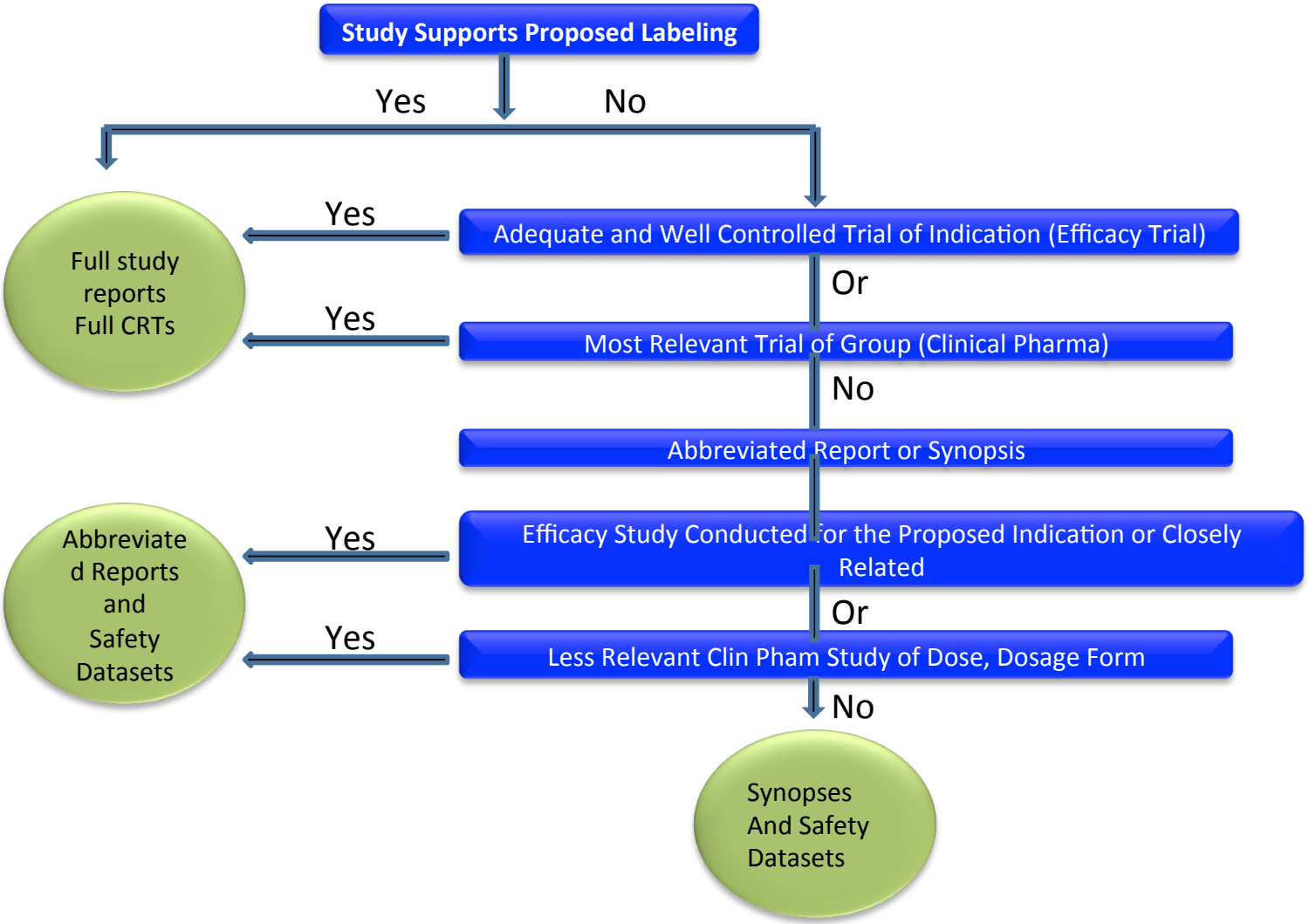
Studies that are not intended to contribute to the evaluation of product effectiveness or provide definitive information on clinical pharmacology, but about which the reviewer needs sufficient information to determine that the study results do not, in fact, cast doubt on the effectiveness claims or the description of the clinical pharmacology.

Abbreviated reports should contain all the *safety information included in a full report*

- Studies with active controls that do not provide the primary or substantiating evidence of effectiveness
- Studies of related indications for which marketing approval is not being sought

- Studies not designed as efficacy studies but that provide significant safety information
- Studies of doses or dosage forms not intended for marketing
- Controlled safety studies

# CSR Format Decision Tree



# Overall Structure of the CSR

1. Title page
2. Synopsis
3. Table of contents for the clinical study report
4. List of abbreviations and definition of terms
5. Ethics
6. Investigators and study administrative structure
7. Introduction
8. Study objectives
9. Investigational plan including Statistical Method
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. References
16. Appendices

# Recommended sections for abbreviated study report

Section 1 - Title page
Section 2 - Synopsis
Section 3 - Table of contents for the individual clinical study report
Section 4 - List of abbreviations and definitions of terms
Section 9.1 - Overall study and design and plan: description
Section 9.8 - Changes in the conduct of the study or planned analyses
Section 10.1 - Disposition of patients
Section 12 - Safety evaluation
Section 13 - Discussion and overall conclusions
Section 14 - Tables, figures and graphs referred to but not included in the text
Section 16.1.1 - Protocol and protocol amendments
Section 16.1.2 - Sample case report forms (unique pages only)
Section 16.3.1 - Case report forms for deaths, other SAEs and withdrawals for AEs
Section 16.4 - Individual patient data listings for safety data. Individual patient listings of efficacy data are *not necessary*

# Appendices Requirement

| Appendix | Full CSR | Abbreviated CSR | Synopsis CSR | Supplemental CSR |
|---|---|---|---|---|
| **Section 16.1.1** Protocol and Amendments | X | X | X | X |
| **Section 16.1.2** Sample Case Report Form | X | X | — | — |
| **Section 16.1.3** List of IECs or IRBs | X | — | — | — |
| **Section 16.1.4** List of Investigators | X | — | — | — |
| **Section 16.1.5** Signatures of Principal or Coordinating Investigator(s) | X | X | X | X |
| **Section 16.1.6** Drug Manufacturing Lot Numbers | X | — | — | — |
| **Section 16.1.7** Randomization Scheme and Codes… | X | — | — | — |
| **Section 16.1.9** Documentation of Statistical Methods | X | — | — | — |

**X** = required; — = optional; Appendices not listed above are also optional

# India requirement

**Schedule Y: Appendix II**

**STRUCTURE, CONTENTS AND FORMAT FOR CLINICAL STUDY REPORTS**

1. Title Page
2. Study Synopsis (1 to 2 pages)
3. Statement of compliance - India- GCP guidelines issued by Central Drugs Standard Control Organization (CDSCO)
4. List of Abbreviations and Definitions
5. Table of contents
6. Ethics Committee
7. Study Team
8. Introduction
9. Study Objective
10. Investigational Plan
11. Trial Subjects
12. Efficacy evaluation
13. Safety Evaluation
14. Discussion and overall Conclusion
15. List of References

# Schedule Y requirement

## 16. Appendices

a) Protocol and amendments
b) Specimen of Case Record Form
c) Investigators' name(s) with contact addresses, phone, email etc
d) Patient data listings
e) Discontinued participants
f) Protocol deviations
g) CRFs of cases involving death and life threatening adverse event cases
h) Publications from the trial
i) Important publications referenced in the study
j) Audit certificate, if available
k) Investigator's certificate

# LEAN or Streamlined Approach

| The CSR should not include: | Rather, the CSR should include: |
| --- | --- |
| • An extensive background section<br>• A complete description of study design and conduct<br>• Detailed statistical methods<br>• Detailed presentations of all results | • Be clear, concise, well organized, and easy-to-read<br>• Be a summary of key results<br>• Reference/link sources for important details<br>• Reference/link detailed analyses provided in Sections 14 & 16 |

This approach meets regulatory requirements.

# Summary

Clinical studies should be reported to the applicable regulatory authorities within 1 year of the time point.

The CSR should be written in a format that is acceptable to all regulatory authorities.

A report should be complete, free from ambiguity, well organized and easy to review

Depending on study types and regulatory authority's requirement, different formats of CSR can be used

# Thank You

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