Clinical Trial Process

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1. Protocol Development

- **Protocol = master plan** of the clinical trial.
- It defines:
  - Objective of the study
  - Study design (e.g., randomized, double-blind, placebo-controlled)
  - Number of subjects
  - Study duration
  - Treatment plan
  - Inclusion & exclusion criteria
  - Endpoints (primary and secondary)

Example:
A protocol may state:

- "Evaluate the efficacy of **Drug X** versus **placebo** in reducing **HbA1c** levels in Type 2 Diabetes patients over 24 weeks."

Who prepares?

- Clinical scientists, physicians, statisticians, regulatory experts.

Next: Protocol is submitted to the **FDA (or EMA/DCGI depending on region)** for review and approval.

2. Regulatory Authority Approval (FDA/EMA/DCGI)

- Regulatory agencies check:
  - Scientific validity
  - Ethical concerns (patient safety first!)
  - Whether risk < benefit

If **approved**, trial can move to the next stage.
If **rejected**, modifications are requested.

Q: Why is protocol approval by FDA important?
A: It ensures the trial is ethical, scientifically valid, and safeguards patient rights before any recruitment begins.

3. Investigator Selection

- Investigators = **doctors/specialists** who conduct the trial at study sites (hospitals, clinics).
- Criteria: experience in the disease area, access to patient pool, facilities for trial (labs, monitoring, etc.).

4. Patient/Subject Recruitment

- **Inclusion Criteria** = who *can* join.
  - e.g., Male/Female aged 18–65, diagnosed with Type 2 Diabetes, HbA1c > 7%.
- **Exclusion Criteria** = who *cannot* join.
  - e.g., Pregnant women, patients with severe kidney failure, or those on conflicting medications.

Who recruits?

- **Clinical Research Associates (CRAs)** and monitors, under investigators' supervision.

5. Clinical Data Management (CDM)

This team ensures data quality, security, and integrity.

A. Data Entry

- Collected in **Case Report Forms (CRFs)**.
- Types:
  1) **Paper CRF** → later entered into system.
  2) **Electronic CRF (eCRF)** → directly entered in **EDC (Electronic Data Capture)** systems (e.g., Medidata, Oracle Clinical).

Example: Patient's visit details, lab results, AEs are entered into eCRF.

B. Data Validation

- **Edit checks** automatically verify correctness.
- Example: Gender can only be "Male" or "Female." If someone enters "Unknown," the system flags an error.
- Other checks: date ranges, lab units, consistency between forms.

Raw datasets are prepared after cleaning.

Q: What is the purpose of edit checks in CDM?
A: To ensure accuracy and consistency of data during entry, preventing invalid or illogical values.

6. Data Analysis

Two main groups work here:

A. Biostatisticians

- Use the **Statistical Analysis Plan (SAP)** — a document specifying which analyses, tests, and outputs are required.
- Responsibilities:
  i. Guide SAS programmers on what outputs to generate.
  ii. Review outputs (Tables, Listings, Figures).
  iii. Interpret and summarize results.

B. SAS Programmers

- Input = cleaned datasets from CDM (in **SDTM format**).
- They create **ADaM datasets** (analysis-ready).
- Generate **TLFs (Tables, Listings, Figures)**.

Examples of Outputs:

- Table: Baseline Demographics (age, sex, BMI).
- Listing: All Serious Adverse Events.
- Figure: Kaplan–Meier survival curve.

Flow:
CDM → SDTM datasets → ADaM datasets → TLFs → Biostat review.

7. Medical Writing Team

- Write **Clinical Study Report (CSR)** based on TLFs/statistician findings.
- Includes:
  - Trial synopsis (what was tested, how, and why).
  - Results (efficacy, safety, adverse events).
  - Discussion (interpretation of findings).

Example:
CSR might state: "Drug X reduced HbA1c by 1.2% compared to placebo, with no major safety concerns."

8. Submission to Regulatory Authorities

- Final CSR + datasets + Define-XML + Review Guides → sent to FDA/EMA/DCGI.

- If approved, drug may progress to next phase or to market.
  Submission Package Includes:
  - SDTM datasets
  - ADaM datasets
  - TLFs
  - Define-XML, ADRG, SDRG
  - CSR

"P-I-P-C-D-A-M-S" → Protocol → Investigator → Patient → CDM → Data Analysis → Medical Writing → Submission.