Introduction in Clinical Trials

- Through the eyes of a statistician -

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Topics

- Context
- History and Regulations
- Conduct of a trial
  - Who is who
  - Protocol
  - Data collection
  - Data management
  - Data review meeting
  - Data analysis
  - Study reporting

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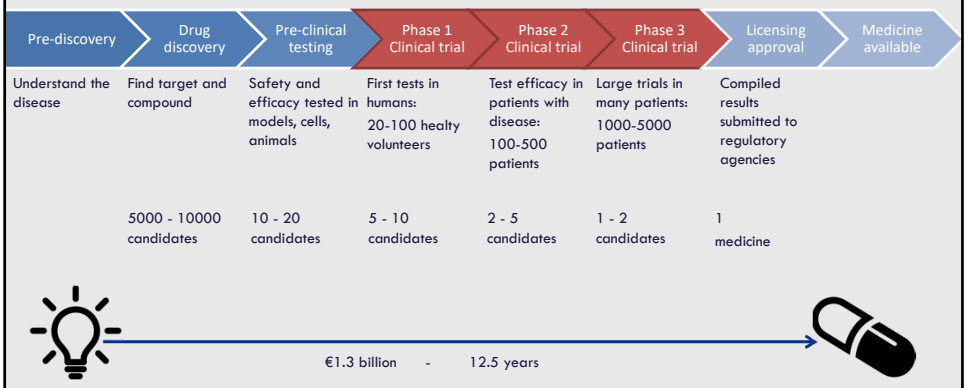
Drug development



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History

Elixir Sulfanilamide (1937)

- No regulatory control ensuring safety of new drugs
- S.E. Massengill company: New preparation of sulfanilamide using diethylene glycol (DEG) as a solvent → "Elixir sulfanilamide"
- Animal testing was not performed
- DEG is poisonous to humans (chief pharmacist was not aware)
- First deaths reported one month after commercialization (+100 deaths in total)

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History

Elixir Sulfanilamide (1937)

- Massengill Company:
  - 'Not responsible'
  - paid minimum fee for naming it 'elixir' while it did not contain alcohol
- Chief Pharmacist comitted suicide

Food, Drug and Cosmetic Act (1938)

- Animal saftey tests are required
- Submission of results to FDA

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History

Nuremberg trials (1945)

- Accusation of doctors involved in unethical human experiments in concentration camps
- No law that differentiated between legal and illegal experiments

Nuremberg Code (1947)

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Nuremberg Code

1. Voluntary consent
2. Beneficial for society
3. Anticipated results justify performance
4. Avoid injury
5. Forbidden if there is a known risk for disabling injury or death
6. Risk-benefit balance
7. Protection of the subject
8. Scientifically qualified staff
9. Subject can always stop
10. Scientist can terminate the trial

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History

Thalidomide (1957)

- Marketed in 1957 by Chemie Grünenthal, as sedative drug and against nausea
- Over-the-counter drug
- Around 10.000 infants born with malformations of limbs
- Withdrawn from the market in 1961

Kefauver-Harris Amendment to the Food, Drug and Cosmetic act

Proof of efficacy, advertising side effects

Declaration of Helsinki

Review of research protocols, informed consent

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History

ICH

- Need for indepent evaluation of medicinal products → realisation was tragedy driven
- Global market: differences in technical requirements → high costs
- ICH: Unified standard for Europe, USA, Japan, Canada, …
  - Safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner

International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use

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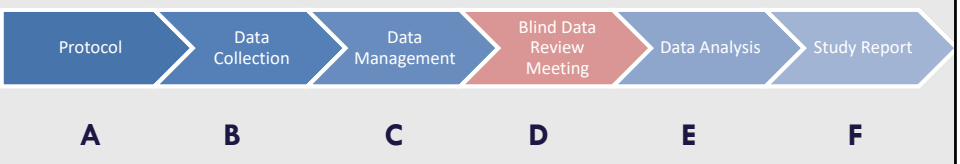
Conduct of a Trial



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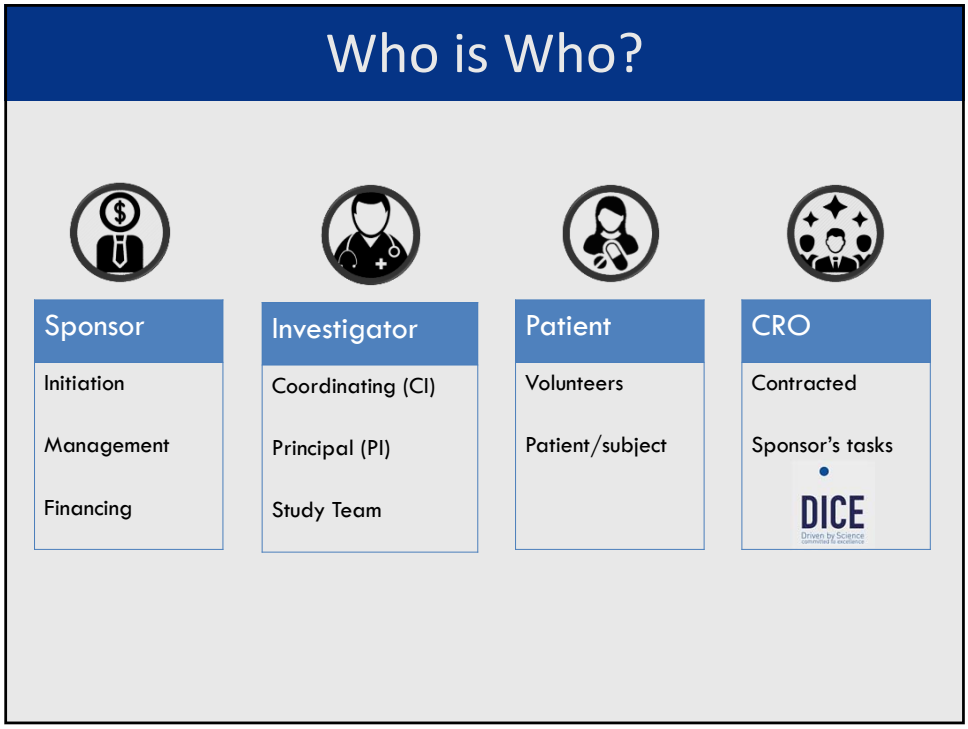
Who is Who?
Sponsor
Initiation
Management
Financing
Investigator
Coordinating (CI)
Principal (PI)
Study Team
Patient
Volunteers
Patient/subject
CRO
Contracted
Sponsor's tasks
DICE

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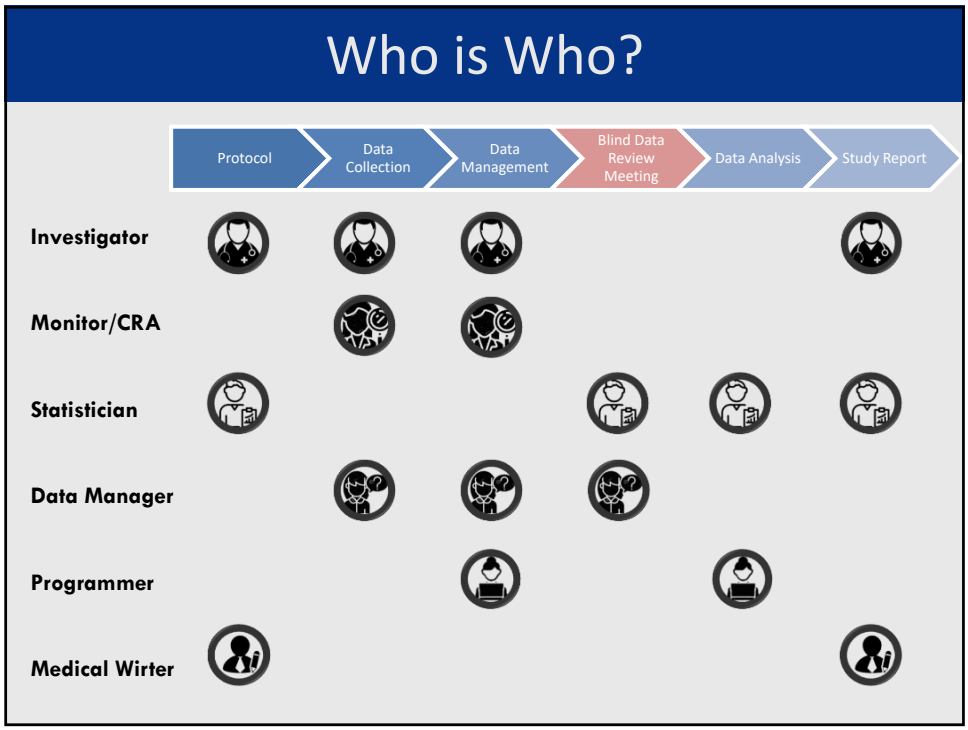
Who is Who?
Protocol
Data Collection
Data Management
Blind Data Review Meeting
Data Analysis
Study Report
Investigator
Monitor/CRA
Statistician
Data Manager
Programmer
Medical Wirter

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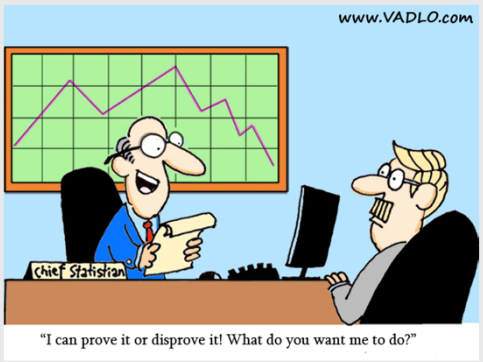
Conduct of a Trial

Protocol → Data Collection → Data Management → Blind Data Review Meeting → Data Analysis → Study Report



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Protocol

ICH E6

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Trial Objectives

- Efficacy / Safety
- Control group
- Superiority / Equivalence
- Endpoints
  - Primary Objective
    - Target variable
    - "Providing most clinically relevant and convincing evidence of the primary objective"
  - Secondary Objectives
    - Supportive

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Trial Objectives

- Characteristics of Endpoints
  1. Objectivity
  2. Frequency
  3. Clinical relevance

A	B	C
Tumor size diameter	Occurence of a stroke	Self-Questionnaire completed by the patient

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Protocol

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Study Design

A. Parallel Group Design
B. Crossover Design
C. Factorial Design

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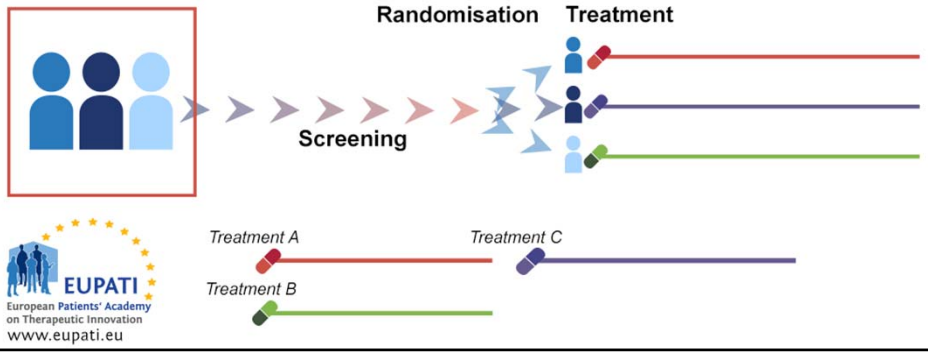
Study Design

Parallel Group Design

Parallel Trial



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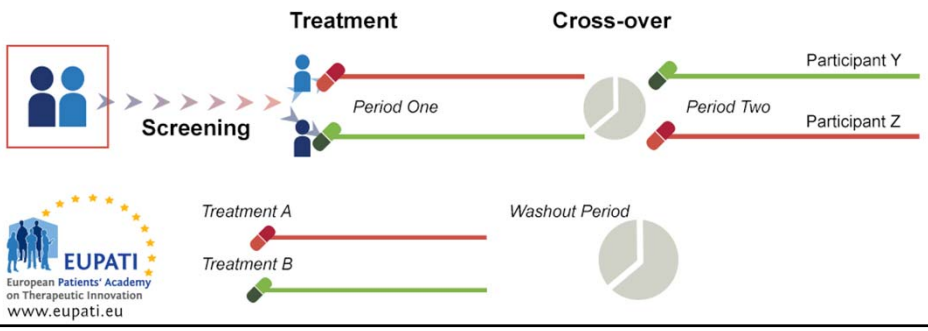
Study Design

Crossover Design

Cross-over Trial



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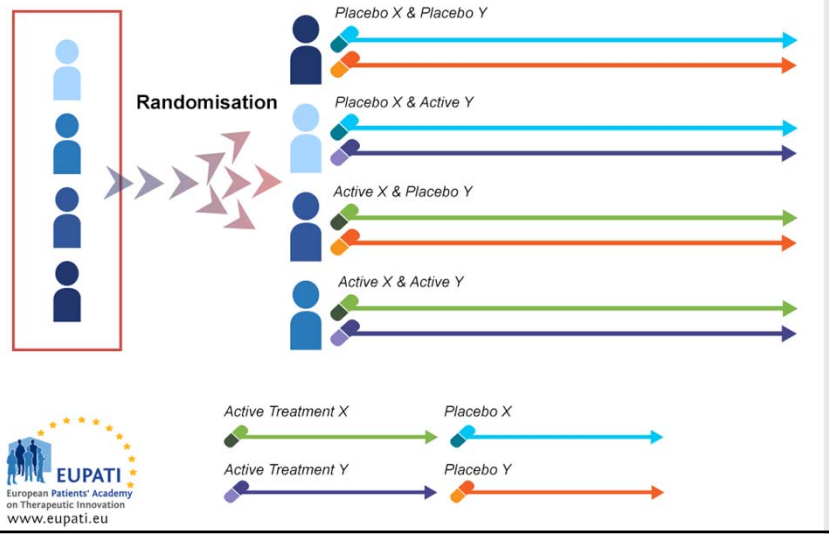
Study Design

Factorial Design



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Study Design

A. Parallel Group Design

A. Crossover Design

A. Factorial Design

1. Protective effect of omega-3 supplement and statins on heart failure
2. Immunochemotherapy in breast cancer
3. Generic drug for hypertension

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Study Design

Avoiding Bias

Bias = Estimate of treatment effect deviates from its true values

- Patients with the most severe symptoms are allocated the experimental treatment
- The treatment group contains on average older patients compared to the placebo group
- Patients on the experimental treatment are followed-up more frequently
- The doctor tends to assess patients on treatment as more healty

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Study Design

Avoiding Bias

Bias = Estimate of treatment effect deviates from its true values

RANDOMIZATION
= Random allocation of treatments to subjects
- Simple
- Block
- Stratified

BLINDING
- Double-blind
- Single-blind
- Open-label

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Study Design

Schedule

	Visit 1[1]	Visit 2[1]	Visit 3	Visit 4	Visit 5
	Screen Day -60 to 0	Day 1 Baseline	Week 4[2] Day 28	Week 8[3] Day 56	Week 12[3] Day 84
Informed consent/assent	X				
Inclusion and exclusion criteria	X	X			
Medical (including acne) history / prior & concomitant medications	X	X			
Collect Demographic Data	X				
Fitzpatrick Skin Type Assessment		X			
Physical Examination(including height and weight)		X			
Vital signs assessment (Blood Pressure & Pulse Rate)	X	X	X	X	X
Update concomitant medications			X	X	X
Urine pregnancy test[4]	X	X	X	X	X
Randomization		X			
Dispense/redispense study product		X	X	X	
Weigh study product bottles prior to dispensing and used bottles upon return		X	X	X	X
Initiate treatment		X			
Dispense/review/ collect study diary		X	X	X	X
Review subject instructions		X	X	X	
Collect empty bottles			X	X	X
Evaluate IGA on face	X	X	X	X	X
Count inflammatory and non-inflammatory lesions on face	X	X	X	X	X
Count inflammatory and non-inflammatory lesions on the chest/back including shoulders (if applicable)		X	X	X	X
Assess for any local cutaneous tolerance[5] on face, and chest/back including shoulders (if applicable)		X	X	X	X
Evaluate Subject's Global Assessment (SGA) on face		X	X	X	X
DLQI or Children's DLQI		X	X	X	X
CADI Questionnaire		X	X	X	X
Evaluate compliance			X	X	X
Adverse event assessment		X	X	X	X
End of study					X

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Protocol

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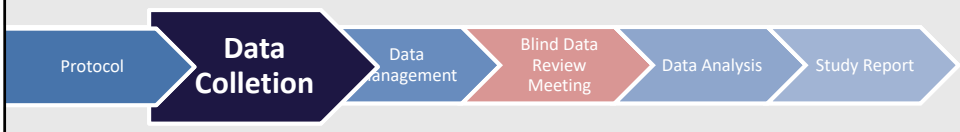
Conduct of a Trial



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Data Collection

1. Approval from Ethics Committe and Competent Authority
2. Selection and training of sites
3. Data collection and monitoring

Case Report Form:

- eCRF
- Paper CRF

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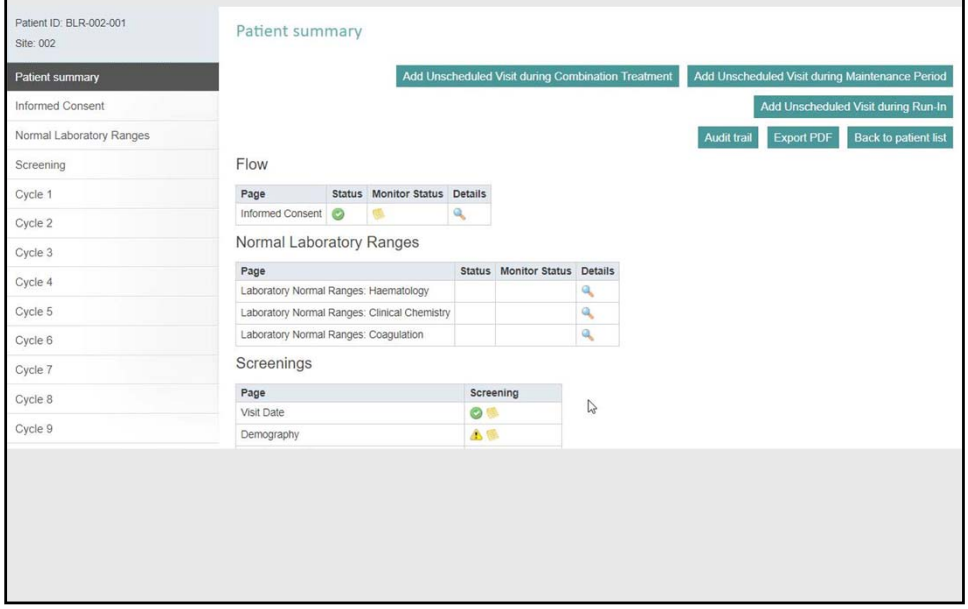
Case Report Form



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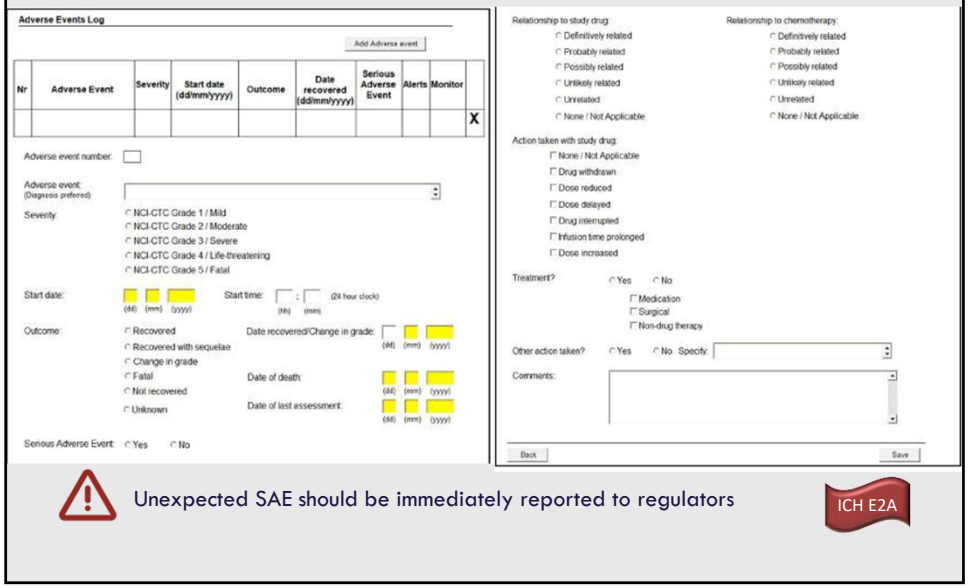
Case Report Form



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Adverse Events

A. An elderly patient suffers from a mild headache for 5 days but is hospitalized for a few days as she is unable to undertake daily activities.

B. A patient attending a hospital visit suffers from a fall, fractures an arm, but is able to return home on the same day after treatment.

C. A patient suffers from influenza and cold whilst taking study drug and has stopped study treatment for 5 days.

D. A patient dies whilst taking placebo

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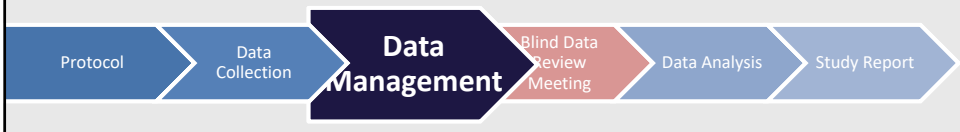
Conduct of a Trial



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Data Management

Before data collection

- Set-up eCRF
- Database design

During/after data collection

- Assure validity and accuracy of the data
  - Automatic edit checks
  - Manual data review
- In case of errors: Query
- Coding
- Reconciliation of external data

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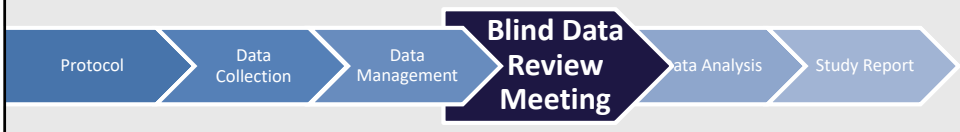
Conduct of a Trial



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Blind Data Review Meeting

- Important milestone
- Identify and evaluate protocol variations
  - Patient not eligible
  - Missing visits/measurments
  - Non-compliance
  - Assessment out of window
  - Prohibited concomitant medication
- Finalize planned analysis: SAP

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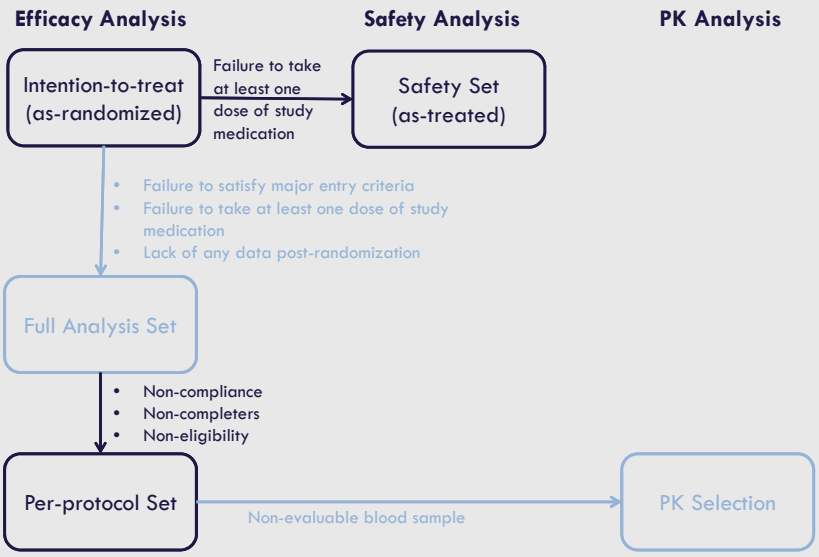
Analysis Sets



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Conduct of a Trial

Protocol → Data Collection → Data Management → Blind Data Review Meeting → **Data Analysis** → Study Report

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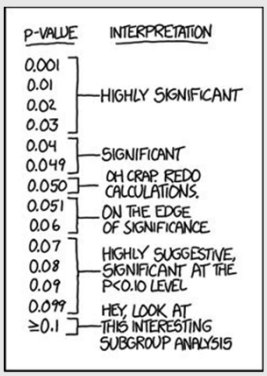
Conduct of a Trial

Protocol → Data Collection → Data Management → Blind Data Review Meeting → Data Analysis → **Study Reporting**



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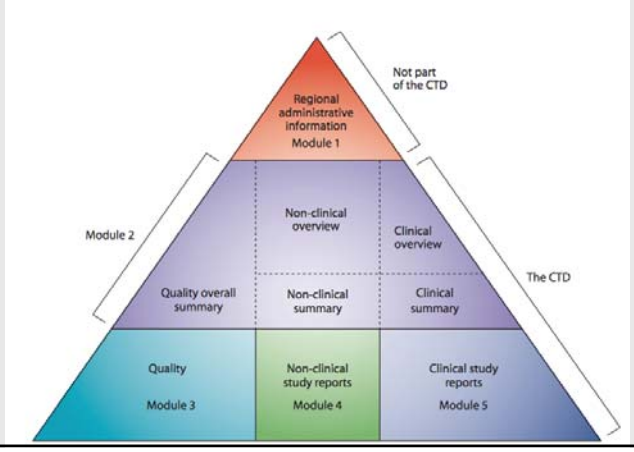
Study Reporting

- Clinical Study Report
- Common Technical Document



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Useful links

- https://www.ich.org/
- https://www.ema.europa.eu/en
- https://www.fda.gov/drugs
- https://www.patientsacademy.eu/

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