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This training and training materials are for educational and informational purposes only.

This training material should be read in conjunction with the applicable latest research policy and regulations from the learner's research organisation and/or institution, Singapore Regulatory Authority and Ministry of Health.

Kindly note that all information and opinions presented in this training and training materials were written to the best knowledge available at the time of writing.

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Module Outline

- What is a Research Protocol
- Basic understanding on the key elements of Research Protocol
  - Protocol Title
  - Trial Objectives & Purpose
  - Study Population
  - Study Design
  - Sample Size

What is a Research Protocol?

The protocol is a plan for a research study:

- **Why** the research is to be done
- **How** the research study will be conducted
- **What** research procedures are to be carried out

If the protocol is well-designed, and the research study is well carried out, the study will generate valid data which supports regulatory decision-making.

CRC should understand what is in a protocol and what to expect when a protocol is received from a sponsor.

Clinical Trial Protocol

A document that describes the **objective(s), design, methodology, statistical considerations,** and **organization** of a trial.

– Consists of background and rationale of the trial

ICH GCP 1.44

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Common Elements of a Protocol

1. Protocol Title
2. Sponsor
3. Background & Rationale
4. Findings from Preclinical Studies
5. Potential Risks & Benefits
6. Trial Objectives and Purpose
7. Subject Population/ Eligibility
8. Trial Design
9. Investigational Product
10. Treatment to be administered
11. Route of administration, dosage, dosage regimen, treatment period
12. Assessment of Efficacy
13. Assessment of Safety
14. Sample Size & Statistical Methods
15. Quality Control & Quality Assurance
16. Ethical Considerations
17. Publications
18. Retention of Trial Documents
19. Funding and Insurance

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Protocol Title

- Summarize the main idea of the clinical trial
- Example:
  - A **randomised**, **double-blind**, **multi-center** **phase III** trial of Drug X in subjects with anxiety disorder

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Trial Objectives & Purpose

- Primary **objectives** and secondary objectives
- Primary and secondary **endpoints** are usually clearly stated in order to satisfy objectives
- Primary endpoints are usually the **key efficacy parameters** to be studied.

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Study Population

Criteria for Subject Recruitment

- Subject inclusion and exclusion criteria (i.e. Eligibility)
- Specified methods to assess and confirm the subject's eligibility

To determine if the subject meets the eligibility criteria for entry into the clinical trial, various tests (e.g. blood test) are done during the screening visit.

A washout period is when subjects are taken off their current (non-study related) medication. When the carryover effect from these medications had time to dissipate, subjects are screened for entry.

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Study Design

Prospective Study

A prospective study follows a cohort of subjects and observes them for the events of interest over a period of time.

Retrospective Study

A retrospective study begins after the events of interest have occurred and the research data are collected from historical records.

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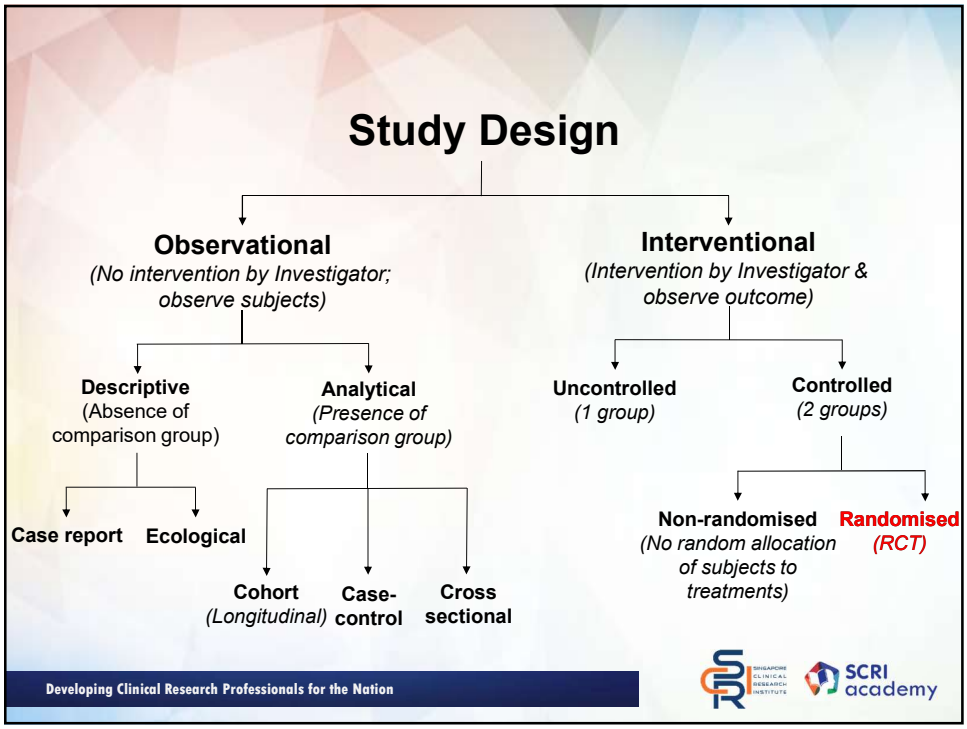

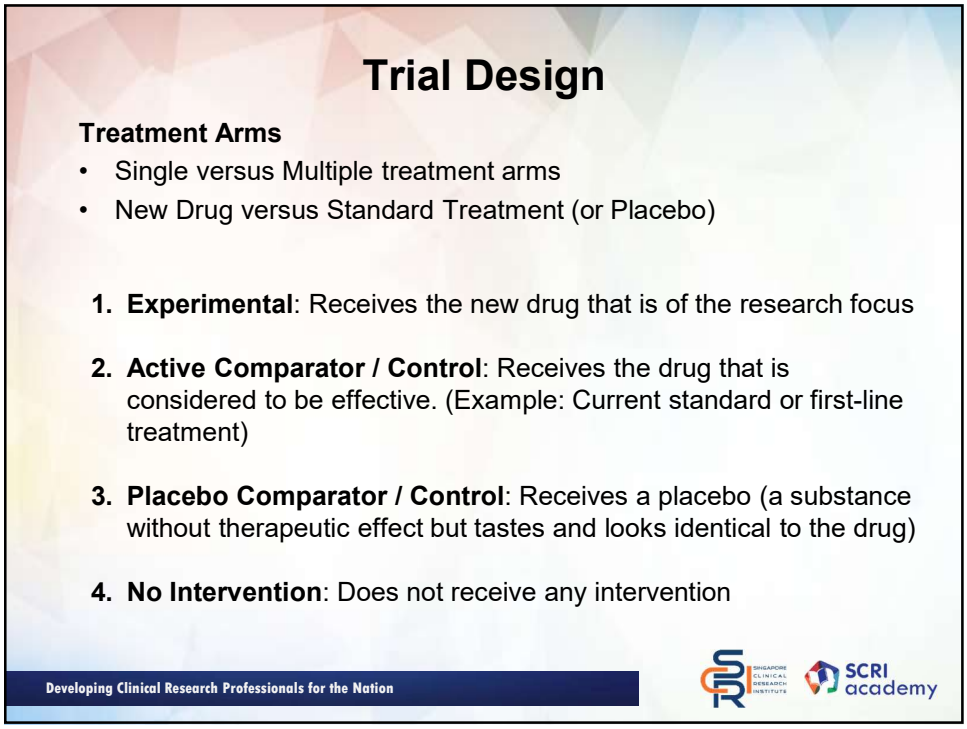

Trial Design

Randomisation

- A technique to reduce the possibility of allocation bias
- Subjects are allocated randomly to different treatment arms

Blinding

- A bias in the subject's response to the treatment can occur if the subject knows which treatment he/she is receiving.
- The research investigator's collection or recording of research data can also be affected if he/she knows the treatment.
- A technique to prevent the subjects and/or investigators from knowing the assigned treatment.
- Prevents the expectations of the participant or investigator from impacting the research results

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Blinding

Double-blinded trial

- Both the subject and the investigator are unaware of the assigned treatment.
- A member of study team (eg: pharmacist) is still aware of the assigned treatment of each subject.

Single-blinded trial

- Subject is unaware of the assigned treatment.

Open label (not blinded)

- Both the subject and investigator are aware of the assigned treatment.

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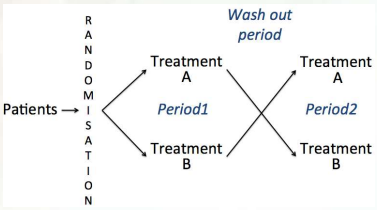
Trial Design

Single vs Multi-centre

Parallel-group vs Crossover

Discontinuation Criteria



Screening Visit prior to Subject Enrollment

- To determine the subject's eligibility to participate in the trial

Study Visits and Study Procedures

- Types of investigations to be performed during the trial
- Expected duration of the subject's participation
- Flowchart of Visits & Events Schedule

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Randomised Controlled Trial (RCT)

- Subjects are allocated randomly to either the intervention group or the placebo (i.e. control) group using a randomisation mechanism
- Ideal when studying the effect of the drug intervention

Advantages	Disadvantages
No population bias	Volunteer biases: group of subjects may not be representative of the whole
Easier to perform blinding	Expensive: money and time
Facilitates statistical analysis	Result does not reveal causation

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Pharmacokinetic & Pharmacodynamic

Pharmacokinetics (PK) is what the Body Does To The Drug.

- How the drug is absorbed, distributed, metabolised and excreted by the body.

Pharmacodynamics (PD) is what the Drug Does To The Body.

- Therapeutic effects or side effects of the drug

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Pharmacokinetic & Pharmacodynamic

PK and PD profiles of a drug are influenced by the drug's physiochemical properties, formulation, route of administration, a patient's disease, drug-drug interactions, food interactions, etc.

It is common during Phase I and Phase II Trials to **collect blood samples at several time points in a short period of time** (before and after drug dosing) for PK and PD testing.

Phase 1 Units and IMUs are set up for accurate collection of PK/PD blood samples at the exact time specified by the protocol.

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The Goal of Trial Design

Right Drug

Right Dose

Right Patient

Right Time

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What is Sample Size?

- The research hypothesis in a clinical trial is based on Statistics.
- Sample size is the number in a **sub-population** to be studied so that we can make an **inference to the actual diseased population**.
- A precise and accurate conclusion can only be drawn from the clinical trial if there is an appropriate sample size.
- Too large a sample size is a waste of time, money and effort.
- Too small a sample size is also a waste of resources because the result becomes invariably inconclusive (i.e. Poor Accuracy).

Meeting Subject Recruitment Numbers ➔ Power of Study

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Key Takeaways

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Important to understand each element of the research protocol thoroughly to avoid protocol deviation.

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Thank you for Completing the

Elements of Clinical Trial Protocol

Online Learning!

References

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- Kent W. Randomisation and blinding in clinical trials. WebmedCentral. CLINICAL TRIALS 2012;3(5):WMC003289
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- Start-up Activities
- Ethics and Study Visits
- Informed Consent
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