Randomized control trials

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- An experiment in which participants in a population are randomly allocated into groups…. to receive , or not to receive … the intervention.
- Most scientifically rigorous method of… hypothesis testing … available .
- Most clear and unbiased evaluation of effect

Unethical issues

- no doubt of efficacy
- Insufficient evidence of the potential for efficacy
- Insufficient statistical power
- Poorly designed trial

- Suited to interventions with modest effect sizes (0.4-0.9) , smaller effect sizes – observational studies

Stages of RCT

- Define the research question
- Identify and recruited the sample
- Apply the intervention at random
- Measure the outcome and compare betweens groups
- Summarise and disseminate the findings

Box 10.2 **Fundamental design issues**

- Thorough review of existing evidence
- Clear hypothesis formulation and statement of objectives
- Informed consent
- Random allocation of intervention
- Use of placebo or active control
- Accurate and careful measurement of potential confounding factors
- Accurate and careful measurement of outcome
- Maximization of follow-up
- Blinding
- Intention to treat analysis
- Unbiased dissemination of findings

Designing RCT

- Thorough review of existing evidence (real doubt about efficacy or effectiveness, complete knowledge of the course and outcome)
- Efficacy studies- “ does this intervention work” , highly selected participants(eg . Exclude , comorbidities) ;so, large effect size , but limited generalisability
- Effectiveness studies –” does this intervention work in real life”

Box 10.5 **Trial development for complex interventions**

(a) Theoretical phase—identifying evidence for the intervention.

(b) Phase I—defining components of the intervention using descriptive studies, and using modeling and qualitative methodologies to understand the components of the intervention and their interaction.

(c) Phase II—defining trial and intervention design including assessment of feasibility, acceptability, what should happen in the control group and even estimating potential effect sizes by carrying out a small scale exploratory trial where outcome measurement can also be tested.

(d) Phase III—the main trial with a detailed protocol development maximising generalizability. Concurrent qualitative work can help to understand why things are happening or not happening.

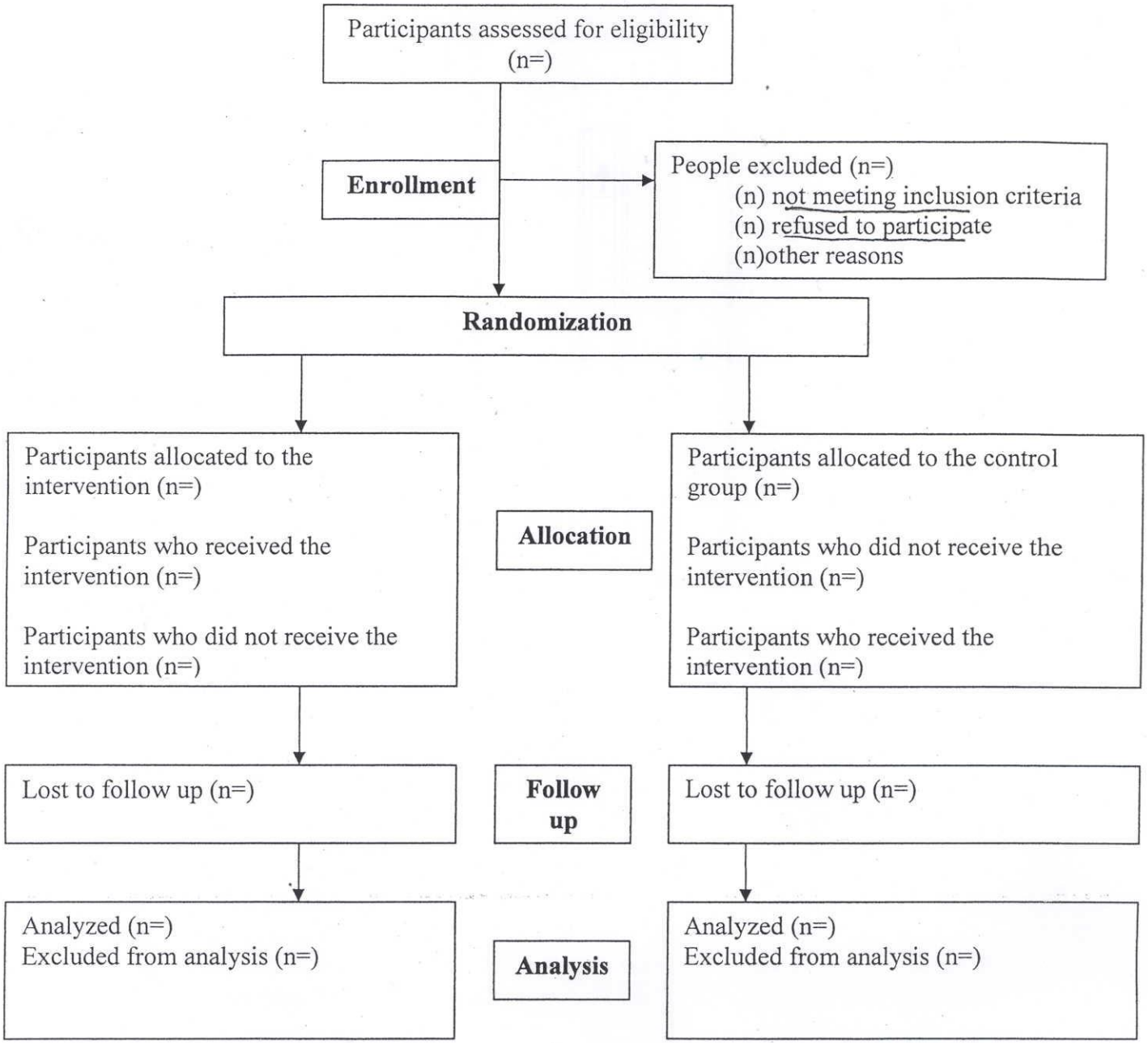
(e) Phase IV—promoting effective implementation putting evidence into practice.

Clear hypothesis formulation and statement of objectives

- Should be one primary hypothesis
- power
- Type I ,II errors

population

- People who would receive the intervention in real life if it proves efficacious
- Inclusion and exclusion criteria
- Many journals now will not publish a trial without a consort flow diagram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Enrollment
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(n) not meeting inclusion criteria
(n) refused to participate
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Lost to follow up (n=)
Follow up
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Analyzed (n=)
Excluded from analysis (n=)
Analysis
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Random allocation of intervention

- Aims – all known and unknown confounders are randomly distributed between control and intervention gr.
- Use of placebo or active control- so that participants and investigators remain blind

Accurate and careful measurements

- Potential confounding factors
- outcome

Maximization of follow up

- Intention to treat analysis- to maintain the power of randomization- all randomized participants is analysed regardless of whether they completed the trial or not
- Dealing with the missing data- last observation carried forward, regression technique, sensitivity analysis

Interpretation of data

- Number needed to treat – no. of people who need to receive the intervention in order to achieve the outcome
- Eg. A study of 20 pt. – 5/10 controls and 7/10 intervention get better
- NNT =1/ risk difference= 1/ 2/10= 5
- You would need to treat 5 people to bring about 1 recovery , attributed to the treatment.

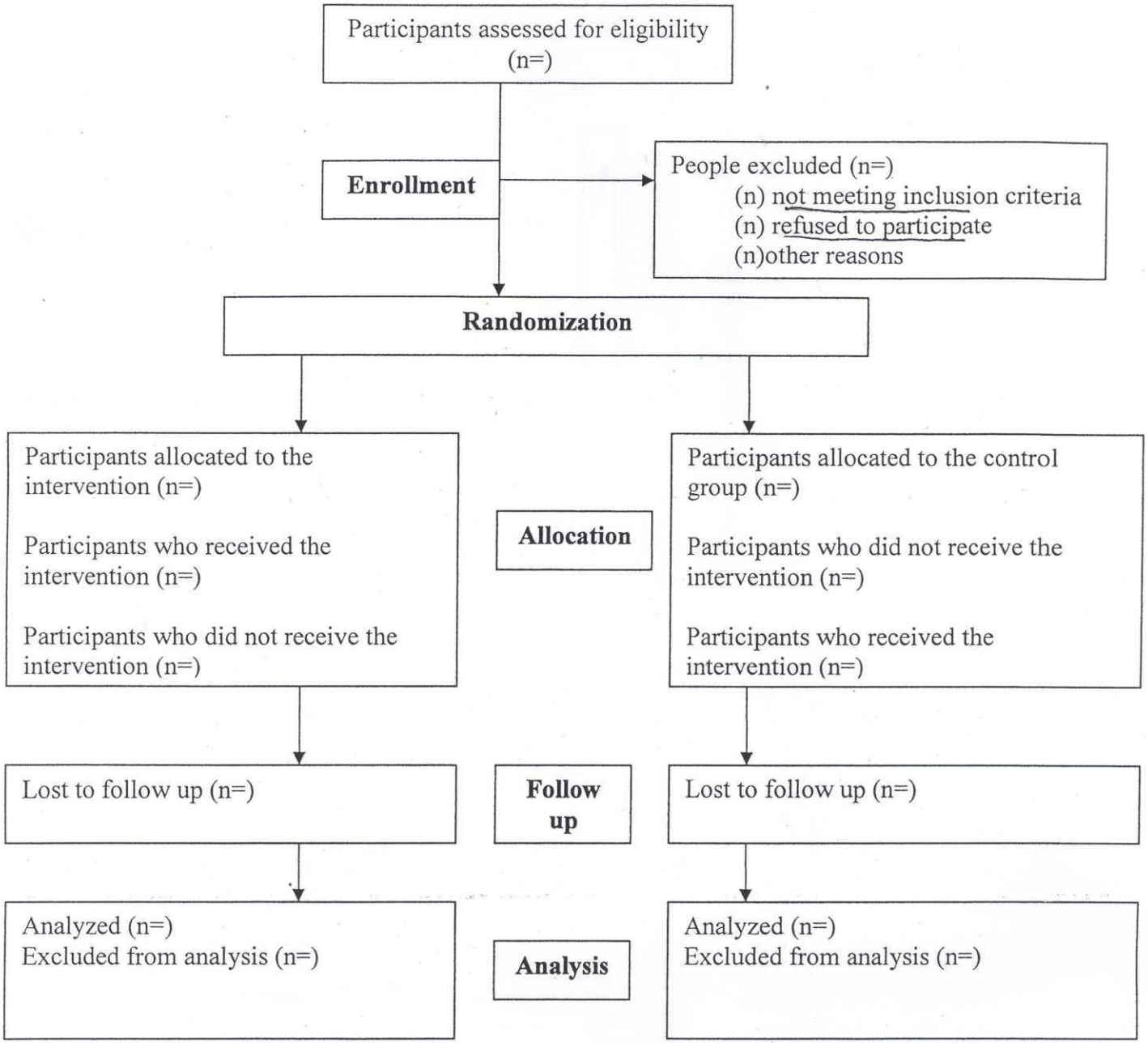
scope of this chapter.

Phase I: Clinical pharmacology and toxicology. This represents the first time a drug is given to humans—usually healthy volunteers in the first place followed by patients with the disorder. The purpose is to identify acceptable dosages, their scheduling and side effects. These are most often carried out in a single centre, requiring 20–80 patients.

Phase II: Initial evaluation of efficacy. These are to determine whether the compound has any beneficial activity. They continue the process of safety monitoring and require close observation, they may be used to decide which of a number of competing compounds go through to Phase III trials. They may be single or multi-centre, and generally require 100–200 patients.

Phase III: Evaluation of treatment effect. This is a competitive phase where the new drug is tested against standard therapy or placebo. There may also be a further element of optimal dose finding. The format for this evaluation is that of an RCT. This phase usually requires large numbers (100s–1000s) and therefore a multi-centre design.

Phase IV: Post-marketing surveillance. Once a drug has been put on the market, there is a need to continue monitoring for rare and common adverse effects including mortality and morbidity. These may only become evident when the drug is used in large numbers in real clinical populations.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