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Study Design: Randomized Controlled Trials (RCTs)

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These slides have been adapted from lecture notes developed by Drs. Alberto Nettel-Aguirre, Sue Ross, and Mat Reeves

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Lecture Objectives

- Principles of the RCT
  - Study sample – including control groups
  - Randomization
  - Blinding
- RCT analysis methods
  - Hypothesis testing
  - Intention to Treat vs Per protocol analysis
  - Effect measures
- Strengths and Weaknesses
- Exercise – design an RCT

To takeaway…

- Principles of the RCT
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  - Intention to Treat vs Per protocol analysis
  - Effect measures

Be familiar, consider elements while reading research papers

- Strengths and Weaknesses → **Know, remember**
- Exercise – design an RCT

To takeaway…

What do you think?

- Strengths and Weaknesses → **Know, remember**

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What is an RCT

- Participants are randomly assigned into either a treatment group or control group and then followed up to observe outcomes
  - The treatment group receives the study intervention (either prophylactic or therapeutic)
  - Control group receives standard treatment, a placebo, or no intervention

- Enables the researchers to make **strong*er* statements regarding causality**

What is an RCT

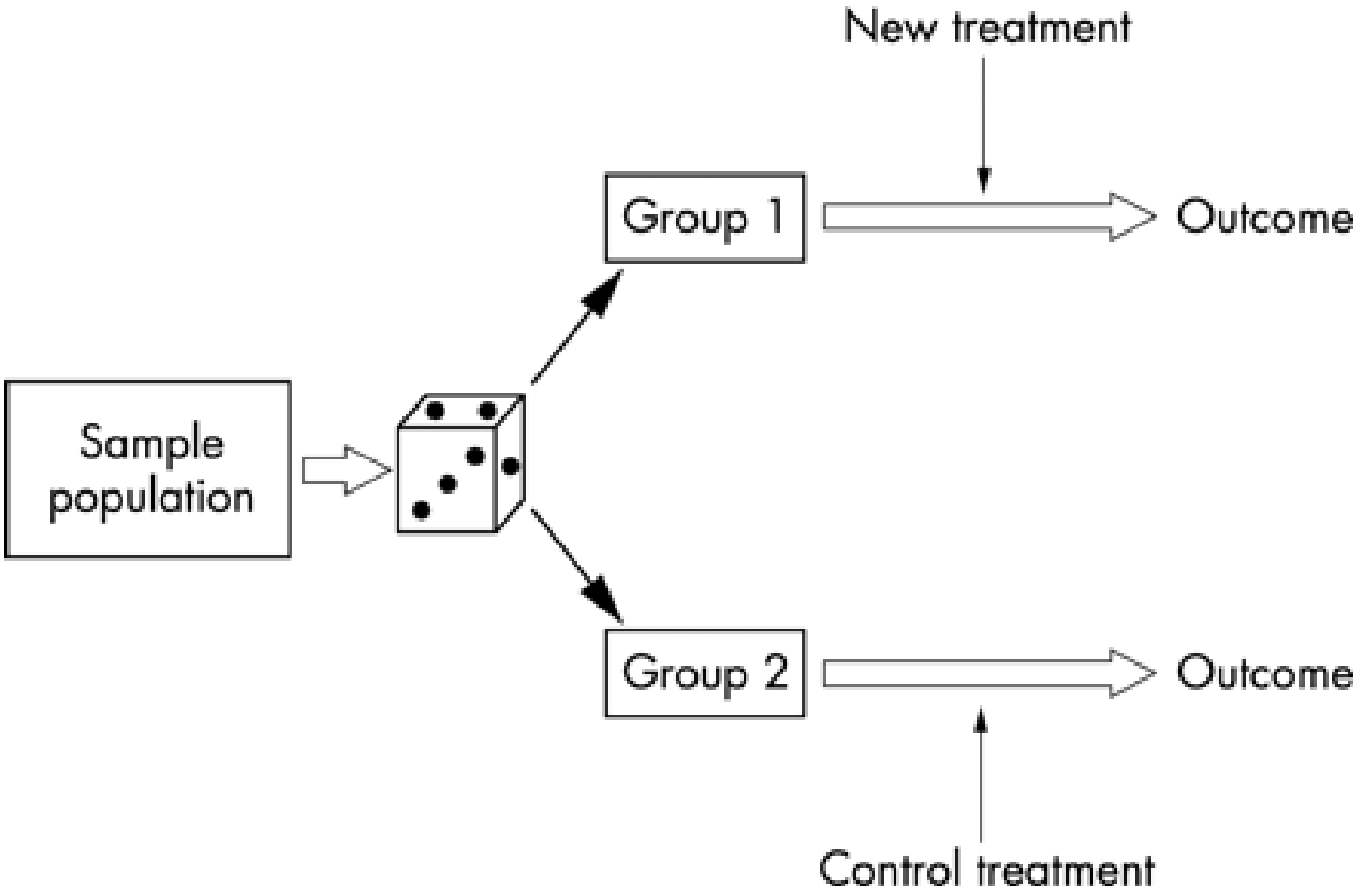
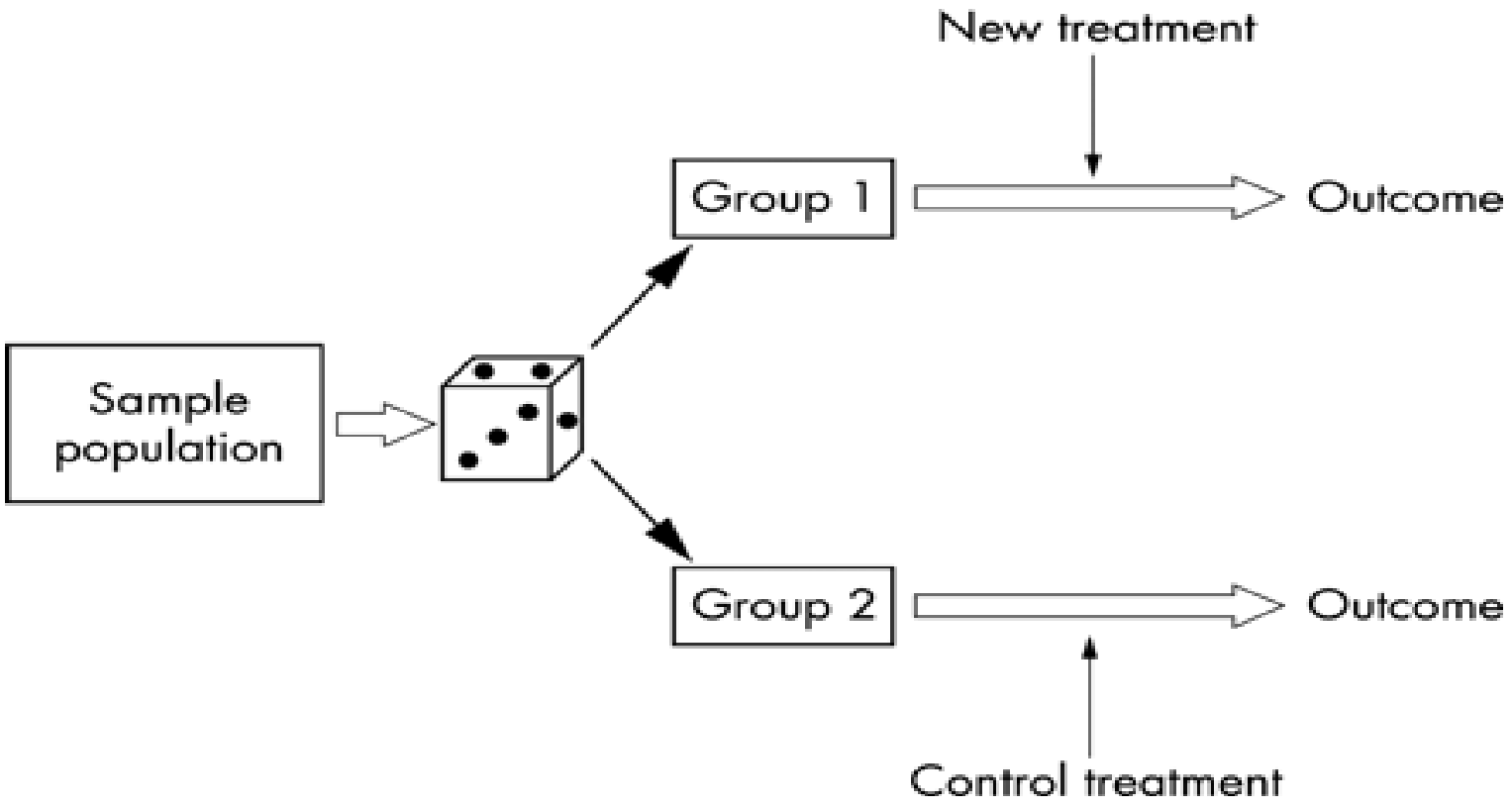


Image taken directly from: Kendall JM. Designing a research project: randomised controlled trials and their principles. *Emergency Medicine Journal* 2003;20:164-168. → Nice summary, recommended reading!

What is an RCT



1. Select Participants: Inclusion and Exclusion criteria
2. Randomization
3. Appropriate treatment and control interventions
4. Follow-up period scientifically relevant
5. Outcome definitions

←----------Across design aspects 1-5: Add blinding if possible----------→

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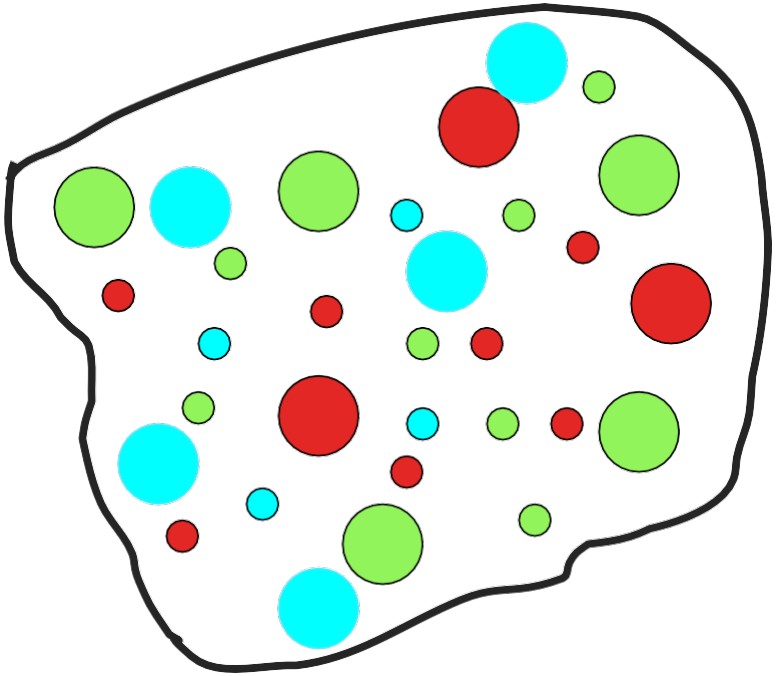
Selection of Participants

Population – ***all*** individuals or items under consideration pertaining to a study question

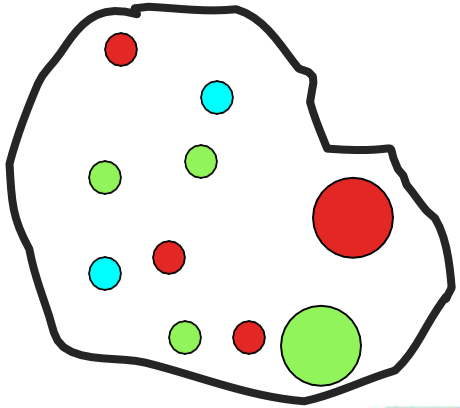
Sample – a selected part of the population from which information is obtained.

RCT question: what is the efficacy and safety of new (circa 2014) Hep C treatments for persons with current or former liver cancer?

Everyone in the world with liver cancer



Persons with liver cancer presenting for treatment at one specialized centre in Cairo



Selection of Participants

- **Deciding on your inclusion and exclusion criteria**
  - *Internal validity*
    - Strong cause-effect conclusions
    - Minimal confounding
    - Usually high → extensive exclusion criteria
  - *External validity*
    - Generalizability of findings
    - Usually limited → extensive exclusion criteria

Try to balance, within reason!

Exclusion criteria needs to be justified!!!

Selection of Participants

- **Historical perspective**
  - Exclusion of all women of child-bearing age from clinical trials post-thalidomide and diethylstilbestrol (DES) in 1950/60s[1]
  - Men were erroneously thought to represent 'the norm'
    - E.g. Low dose aspirin to prevent first myocardial infarction[2]
- **Current context**
  - Underrepresentation of women, older people, ethnic minorities
  - 'Protection by exclusion' → contemporary examples?

1) Lippman A. The Inclusion of Women in Clinical Trials: Are we asking the right questions? Women and Health Protection. March 2006. Published online at: https://whp-apsf.ca/pdf/clinicalTrialsEN.pdf
2) Ridker PM, Cook NR, Lee IM, et al (2005). A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *NEJM* 352:1293-1304.

Selection of Participants

- **"Acceptable" exclusions**
  - **Ethical:** risk of treatment (or non-treatment) is unacceptable
  - **Complex participants:** very severe disease, already received treatment (or related treatment), comorbidities
  - **Perceived follow-up difficulties:** Likely non-adherence, language barrier, other practical (e.g. no phone)

All will penalize external validity!

- E.g. exclusion of elderly persons, persons with former liver cancer, persons with cirrhosis from Hepatitis C direct acting antiviral trials

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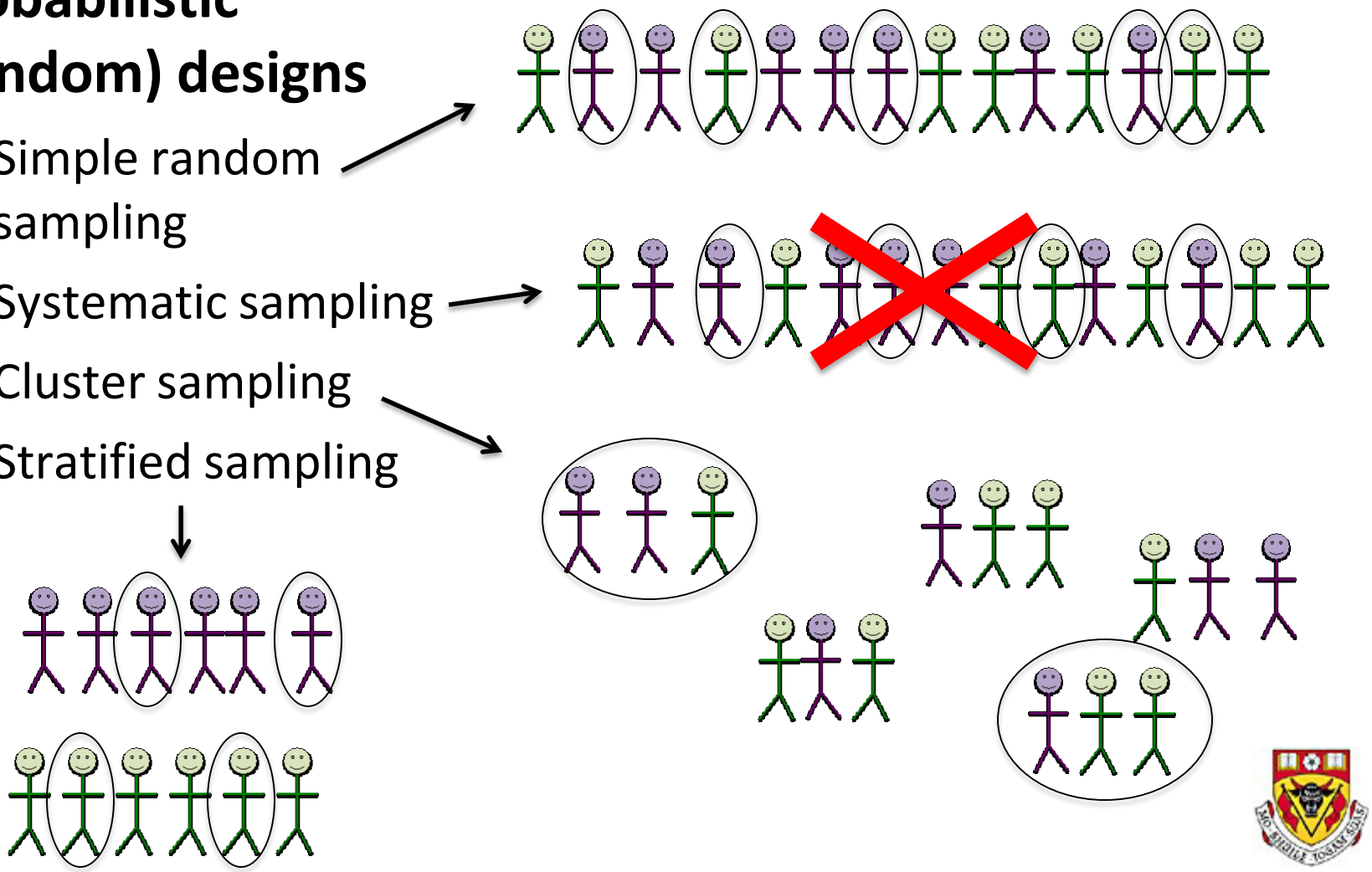
Randomization

- **Good randomization = balanced participant characteristics**
  - Accounts for measured and unmeasured confounding
  - **Unpredictable -** E.g. coin toss, concealed envelopes using randomization matrix
  - **Reproducible -** State methods clearly
  - **Free from manipulation**

Sampling Designs

- **Probabilistic (random) designs**
  - Simple random sampling
  - Systematic sampling
  - Cluster sampling
  - Stratified sampling

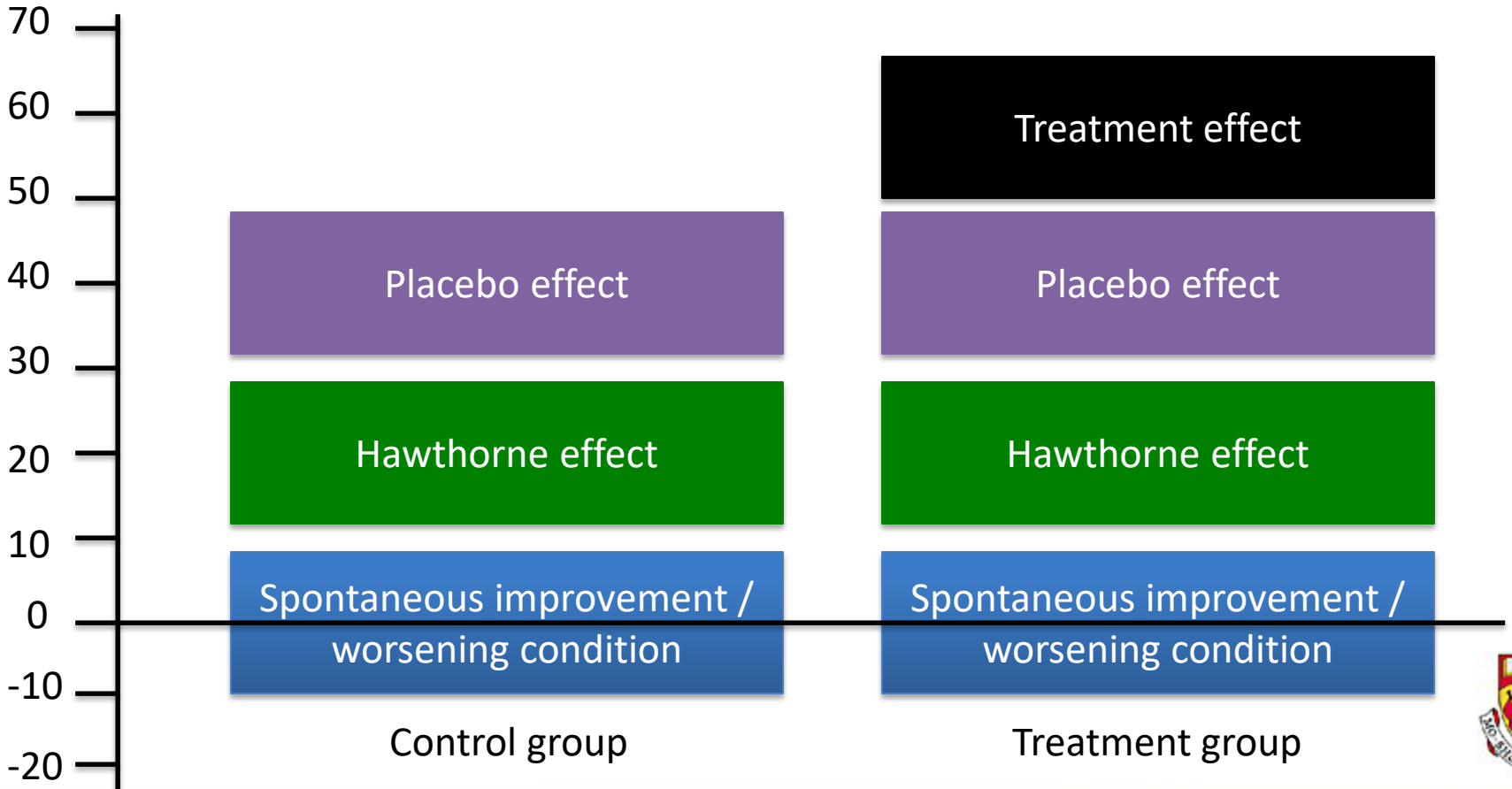


The intervention – treatment group

- **Therapy / prophylactic under investigation**
  - *Ethical considerations*
    - Side effects regardless of outcome - use “lowest effective dose”
    - Truly unknown superiority - is non-administration acceptable?

The intervention – control group

- **Placebo / standard treatment / no treatment**
  - Allows for quantification of actual treatment effect size



Blinding

- **No blinding = "open-label"**
  - E.g. surgical intervention
  - E.g. standard treatment w/ different schedule

- **IDEALLY blinding of:**
  - Participants
  - Caregivers / attending clinician
  - Data (outcome, other) collection personnel
  - Outcome adjudicators, data analysts

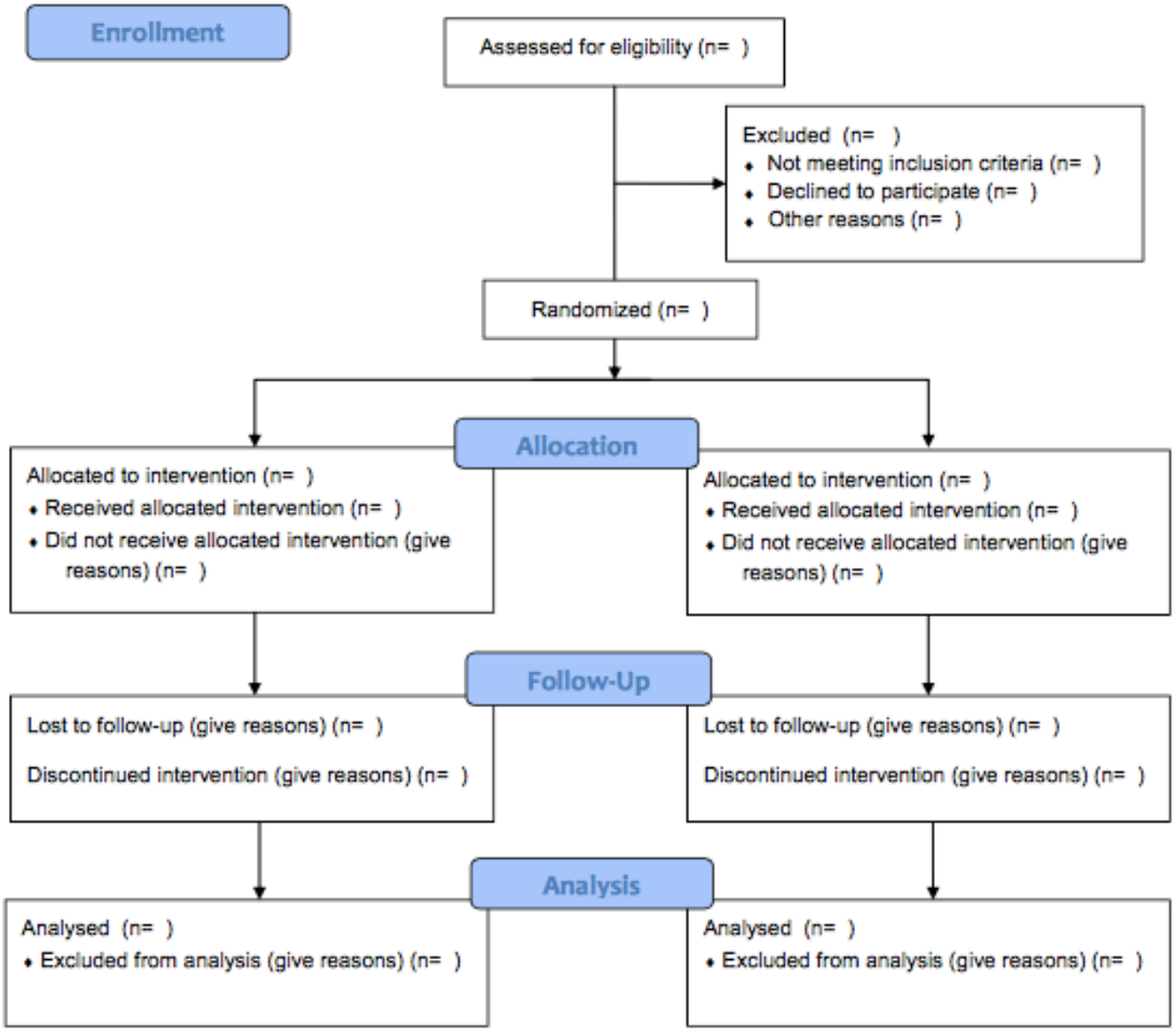
Prevent performance bias!

Prevent detection bias!

Follow-up and loss-to-follow-up (LTFU)

- **Length of follow-up → appropriate for outcome**
- **Loss-to-follow-up (LTFU)**
  - How might LTFU participants differ from those who remain?
  - Not missing at random
- **Poor compliance to treatment**
  - Including cross-over (known or unknown to study personnel)
  - How might these participants differ from others?
- **‘5 and 20’ rule:**
  - <5% is limited bias, >20% is a high threat to study validity
- **Sensitivity analyses** (e.g. best *vs* worst case scenario)

CONSORT (guideline) RCT Flowchart



Accessible at: http://www.consort-statement.org/Media/Default/Downloads/CONSORT%202010%20Flow%20Diagram.pdf

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Statistical Analysis of RCTs

Write a statistical analysis plan before hand!

- *Specify:*
  - Hypothesis
    - Non-inferiority
    - Equivalence
    - Superiority
  - Sample size calculation (based on hypothesis)
  - Outcome definitions
    - Adverse events monitoring!
    - Stopping rules
  - Model choice and variables to include
    - Intention to treat (ITT) versus per-protocol analysis (PPA)
  - Subgroup analyses
  - Sensitivity analyses

RCT Statistical Analysis – Hypothesis

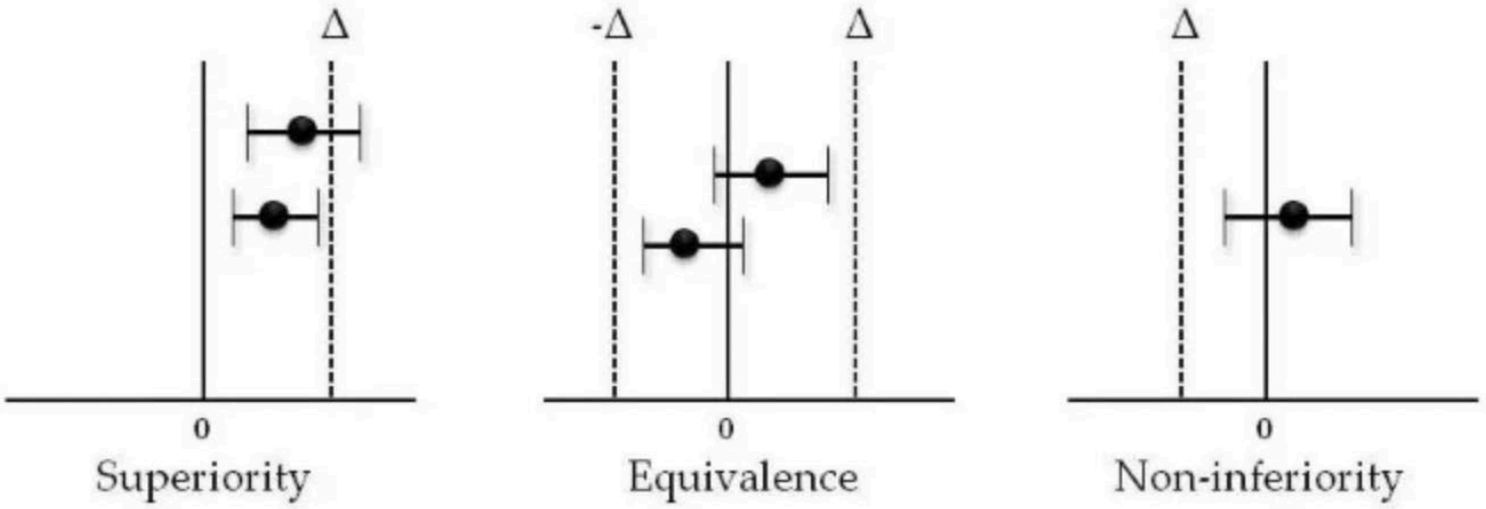
Hypothesis testing

- Non-inferiority
  - New treatment ≥ Old treatment
  - Minimum level of efficacy (“at least the same benefit”)
- Superiority
  - New Treatment > Old Treatment
  - Demonstrate a clear effectiveness (or increased effectiveness)
- Equivalence (or bioequivalence)
  - New treatment = Old treatment +/- acceptable difference
  - E.g. approval of generics, cost-effective interventions

Sample size will be based on type of hypothesis, as well as specified parameters (i.e. clinically relevant amount of superiority)

RCT Statistical Analysis – Hypothesis

Figure 1



The role of Δ in superiority, equivalence and non-inferiority trials.

Schumi J, Wittes JT. Through the looking glass: understanding non-inferiority. *Trials*. 2011 Dec;12(1):1-2.

RCT Statistical Analysis - Outcomes

- **Outcome definitions**
  - *Quantitative change in condition:* e.g. % virus cleared, increase in ALT, change in quality of life
  - *Events-based*: negative (.e.g. death, disease progression), positive (e.g. remission, 'undetectable virus')
  - Poorly defined outcomes = threat to study validity

- **Adverse event monitoring**
  - Related or not-related to study treatment
  - Severe (SAE) vs non-severe (AE) adverse event
  - Adverse reaction

- **Stopping rules:** based on interim analysis (clear superiority or inferiority) or adverse reactions

RCT Statistical Analysis – ITT vs PPA

Intention to Treat (ITT)

- Participants are analyzed within the group (treatment vs control) that they were randomly allocated to
  - Regardless of protocol violations
    - Protocol violations = took no treatment (ineligible, early drop-out), cross-over or contamination, loss-to-follow-up
  - How to consider missing outcomes?
    - Imputation (fancy methods, treatment failure), as missing
- **Conservative, gold standard**

RCT Statistical Analysis – ITT vs PPA

Per protocol analysis (PPA)

- Compliant participants are analyzed
  - Protocol violations are excluded
    - Regardless of initial randomization = As Treated (AT)
  - How to consider missing outcomes?
    - Complete case analysis
- **Biased, especially if high % protocol deviations, BUT often used → can be appropriate as a sensitivity analysis**

Generally, researchers are confused about which approach they have actually used!

ITT vs PPA: Example

Comparison of surgical treatment with medical (standard of care, no surgery) among 768 men with stable angina pectoris. Only 767 received treatment.

Table: Effect of different analysis approaches on an RCT of coronary artery bypass surgery versus medical treatment in 767 men with stable angina. (Lancet 1979;i:889-93).

	Allocated (vs. actual) treatment				
	Medical (medical)	Medical (surgical)	Surgical (surgical)	Surgical (medical)	ARR (95% CI)
Num. subjects	323	50	368	26	
Deaths	27	2	15	6	
Mortality (%)	8.4%	4.0%	4.1%	23.1%	
ITT analysis	7.8% (29/373)		5.3% (21/394)		2.4% (-1.0, 6.1)
PP analysis	8.4% (27/323)		4.1% (15/368)		4.3% (0.7, 8.2)
AT analysis	9.5% (33/349)		4.1% (17/418)		5.4% (1.9, 9.3)

AT= as treated analysis, ARR = absolute risk reduction

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RCT Statistical Analysis – Measures of Effect

- Benefit of RCTs – simple and robust analysis
  - Risk ratio (RR)

$$\frac{\text{Risk of outcome in treatment group}}{\text{Risk of outcome in control group}}$$

  - Risk difference (RD)

    Risk of outcome in treatment group - Risk of outcome in control group

  - Hypothesis testing
    - Comparison of two independent samples proportions (dichotomous outcome) : Chi-square or Fisher's exact

RCT Statistical Analysis – Measures of Effect

- **Other approaches**
  - Binomial regression (risk ratios)
  - Logistic regression (odds ratios)
  - Poisson regression (rate ratios)
  - Survival analysis
    - Time to event Kaplan Meier life table approach
    - Cox Proportional Hazards Regression (hazard ratios)

RCT Statistical Analysis – Other

- **Subgroup analyses**
  - Is there a difference in effect by gender? sex? age? --> Stratify!
  - Pre-specify in statistical analysis plan

- **Sensitivity analyses**
  - Intention-to-treat versus modified intention-to-treat versus per-protocol
  - Various types of imputation for missing data

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Summary – RCT Strengths

- Controls for known and unknown confounding
  - *If* high compliance, low loss-to-follow-up
- Allocation concealment and blinding controls for bias
- Simple, robust analysis techniques

Summary – RCT Weaknesses, Threats

- Ethical issues
  - Potential exposure to harm
- Expensive and complicated to carry out
- Low external validity (limited generalizability)
- **Threats to internal validity (how to mess up an RCT…)**
  - Compliance to protocol (including managing lost-to-follow-up)
  - Open label vs single / double / triple blind
  - Poor outcome definitions
  - Statistical analysis plan – including ITT versus PPA analysis!

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Exercise – Option 1

Monoclonal antibodies targeting interleukins have shown to be effective in treating severe asthma. However, current therapies of this nature are not effective for all persons (some patients/participants continue to experience severe symptoms). New therapeutic monoclonal antibody targets are needed.

Design a trial to determine the effectiveness of a new therapy of this type (lets call it 'Monoclonal Antibody X') given to adults with severe asthma to prevent asthma exacerbations / reduce asthma symptoms.

Exercise – Option 2

The success of the COVID-19 vaccine depends on mass participation. However, approximately 10% of population X is hesitant to receive the COVID-19 vaccine. Current public health messaging about vaccines and vaccine safety may not be effective.

Design a trial to determine the effectiveness of varying public health messaging strategies (e.g. types of information, ways of giving information) to reduce COVID-19 vaccine hesitancy in participants.

Exercise – Tips

Things to include:

- Setting (sample population)
  - Inclusion and exclusion criteria

- What will be the intervention, what will be the 'treatment' of the control group

- Randomization strategy used

- Blinding – to what extent?

- Length of follow-up, primary outcome definitions

- Analysis (optional) - what type of hypothesis? What effect measure would be most interesting / best for communicating your results