Community interventions (cluster randomised) and equivalence trials

Gilda Piaggio

UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction
World Health Organization

Geneva, March 2003

Introduction

Types of studies based on the objectives:

- Descriptive
- Comparative: estimation and test of hypothesis about the effect of a treatment or exposure on an outcome
- Model building

We will consider comparative studies

Introduction

Types of comparative studies:

- Cross-sectional study
- Cohort studies
- Case-control studies

} Observational

- Experimental studies → Clinical trials

Introduction

Types of controlled clinical trials:

- Non-randomised
- Randomised
  - Individually randomised
  - Cluster randomised
  - Simple randomisation
  - Restricted randomisation

Introduction

Gold standard of clinical research:

- Randomisation
  - reduces selection bias
  - theoretical basis for analysis
- Concealment
  - for successful randomisation
- Blinding
  - prevents bias after treatment assignment

Cluster randomised trials

Cluster randomised trials are experiments in which social units or clusters rather than individuals are randomly allocated to intervention groups.

Examples of social units and interventions:

- Communities and mass education programs
- Clinics or hospitals and medical interventions
- Schools and smoking prevention programs
- Families and dietary interventions

Cluster randomised trials (contd.)

Why using cluster randomised design?

- Administrative convenience or necessity
- To reduce intervention contamination
- To increase compliance
- To avoid ethical problems

Cluster randomised trials (contd.)

Disadvantages of the cluster randomised design

- Reduction in effective sample size, extent depending on degree of within-cluster correlation (ρ) and on average cluster size (m)

The design effect is

$$DE = 1 + \rho\,(m - 1)$$

Cluster randomised trials (contd.)

Disadvantages of the cluster randomised design

- Standard approaches for sample size estimation lead to underpowered studies
- Standard approaches for statistical analysis tend to bias p-values downwards and give spurious statistical significance
- When clusters are large (communities), the number of clusters that can be studied tends to be small

Cluster randomised trials (contd.)

Reasons for between-cluster variation:

- Subjects frequently select the clusters to which they belong: patient characteristics could be related to age or sex differences among physicians
- Important cluster characteristics affect all individuals within the same cluster in the same manner: differences in temperature between nurseries maybe related to infection rates
- Individuals within clusters frequently interact and may respond similarly: education strategies or therapies provided in a group setting

Cluster randomised trials (contd.)

In cluster randomised trials, unit of analysis and unit of randomisation can be different, depending on the level of inference:

- Inference at the individual level: Example: Antenatal Care Trial used clinics as the unit of randomisation, women as the unit of analysis
- Inference at the cluster level. Example: in the Second Opinion Trial, inference was intended at the hospital level

Cluster randomised trials (contd.)

Most common designs in cluster randomised trials:

- Completely randomised: clusters allocated at random to the interventions
- Matched pairs: clusters are paired, and the two clusters within each pair are allocated at random to the two interventions
- Stratified: clusters are grouped in homogeneous strata, and the they are allocated at random to interventions

Cluster randomised trials examples: The Aceh study

(Ref: Abdeljaber et al, Amer J of Public Health 1991)

- Purpose: Evaluate the effectiveness of vitamin A supplementation on symptoms of respiratory and enteric infections among Indonesian children aged 1-5 years
- Design: completely cluster randomised
- Unit of randomisation: villages (about 64 children per village)
- Number of villages per intervention group: 229 intervention villages and 221 control villages
- Primary outcome: 1-year prevalence of cough, fever and diarrhoea

Cluster randomised trials examples: The COMMIT Community Intervention Trial

(Ref: COMMIT Research Group, Amer J of Public Health 1995)

- Purpose: promote smoking cessation using a variety of community resources
- Design: matched pairs clusters
- Unit of randomisation: communities (about 500 heavy smokers per community)
- Number of communities per intervention group: 11
- Primary outcome: 5-year smoking cessation rate among heavy smokers

Cluster randomised trials examples: The Antenatal Care Trial

(Ref: Villar et al, Lancet 2001)

- Purpose: to compare the standard model of antenatal care with a new model that emphasises actions known to be effective in improving maternal or neonatal outcomes and has fewer clinic visits
- Design: stratified cluster randomised (strata based on countries and clinic characteristics)
- Unit of randomisation: clinics (463 women recruited by clinic, on average)

Cluster randomised trials examples: The Antenatal Care Trial

(Ref: Villar et al, Lancet 2001)

- Number of clinics per intervention group: 27 new model clinics, 26 standard model clinics (12 clinics randomly assigned in each of three countries, 17 in one country)
- Primary outcomes: low birthweight (<2500 g), pre-eclampsia/eclampsia, severe postpartum anaemia (<90g/L haemoglobin) and treated urinary tract infection

Cluster randomised trials examples: The CATCH Trial (Child and Adolescent Trial for Cardiovascular Health, Ref: Luepker et al, JAMA 1996)

- Purpose: to assess the effect of health behaviour interventions, focusing on the elementary school environment
- Design: stratified cluster randomised (strata were four cities in the United States)
- Unit of randomisation: elementary schools
- Number of schools per intervention group: 48 (24 schools randomly assigned in each of the four strata)
- Primary outcome: serum cholesterol change after 3 years of follow-up

Equivalence trials

In **superiority trials**, we seek to show evidence in favour of a difference.

- Null hypothesis: there is no difference between treatments
- Alternative hypothesis: there is a difference

In **equivalence trials**, we seek to show evidence in favour of no difference.

- Null hypothesis: there is a difference of at least Δ
- Alternative hypothesis: a difference if exists, is less than Δ

Δ is the margin of equivalence

Equivalence trials

When to use equivalence trials:

A treatments has advantages in terms of side-effects, cost or preference. It is to be recommended if the efficacy is equivalent

Equivalence trials examples: The Yuzpe-levonorgestrel trial

(Ref: Task Force on Postovulatory Methods of Fertility Regulation, Lancet 1998)

- The Yuzpe regimen for emergency contraception is associated with side-effects like nausea and vomiting
- Levonorgestrel is better tolerated
- If equally or more effective, it would be preferred compared to Yuzpe

Equivalence trials examples: The Antenatal Care Trial

(Refs: Villar et al, Lancet 2001
Piaggio et al, Statistics in Medicine 2001)

- Provision of routine antenatal care by the new model implies a reduction in cost and can be implemented without resistance from women
- It seems not to affect maternal and perinatal outcomes
- Then it is recommended

Equivalence trials examples: Prostaglandins for prevention of postpartum haemorrhage

(Ref: Gülmezoglu et al, Lancet 2001)

- Oxytocin in the management of third stage of labour is administered by injection, requires refrigeration and protection from light
- Misoprostol, if equally effective, could be an alternative

Effectiveness was defined in terms of the outcomes

- measured postpartum vaginal blood loss of 1000 ml or more
- need for additional uterotonics

Equivalence trials (contd.)

In **superiority trials**, a significant difference is evidence in favour of the alternative hypothesis

In **equivalence trials**, a significant difference might be compatible with equivalence or with no equivalence.

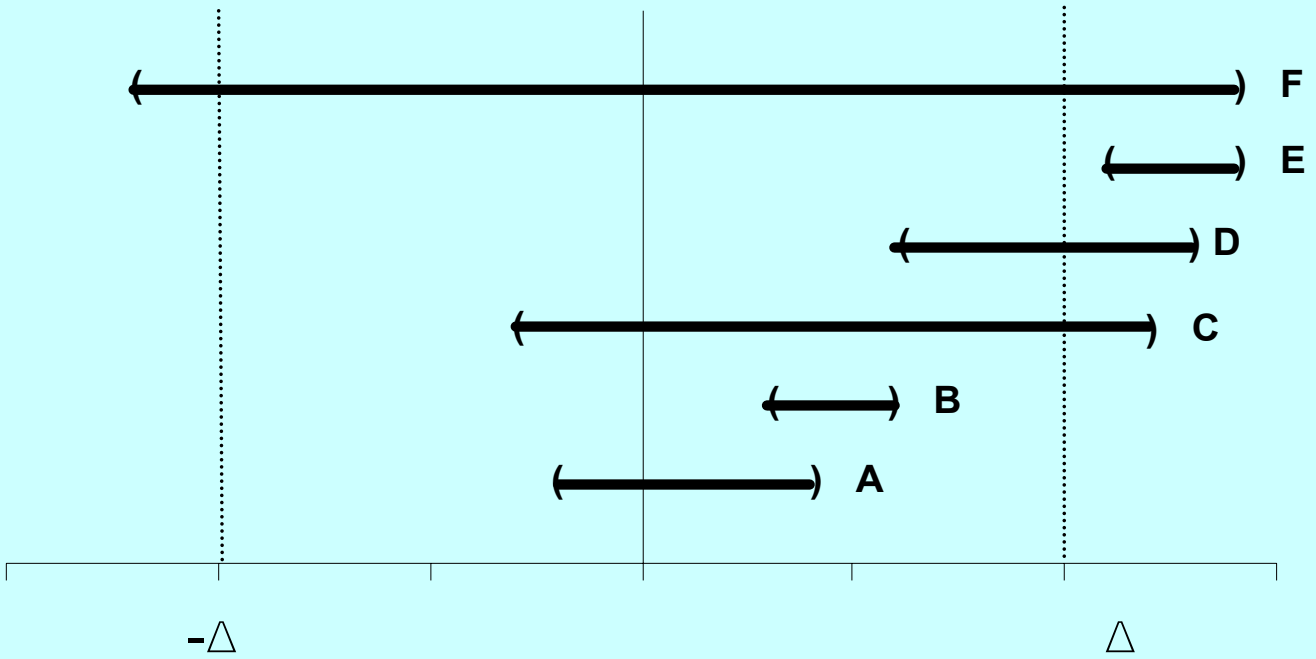
Lack of significance is no evidence of equivalence

Equivalence trials (contd.)

To assess equivalence, we use confidence intervals (CI):

- If the 95% CI lies entirely within the preset margin of equivalence Δ, equivalence is demonstrated
- If the 95% CI lies entirely outside the preset margin of equivalence Δ, non-equivalence is demonstrated
- If the 95% CI lies crosses the preset margin of equivalence Δ, the results are inconclusive

Equivalence trials (contd.)



Equivalence trials (contd.)

Equivalence trials are usually larger than superiority trials:

Calculation of sample size uses a different formula

Refs:

Makuch R and Simon R. Sample size requirements for evaluating a conservative therapy. Cancer treatment reports 1978, 62:1037-1040.

Jones B, Jarvis P, Lewis JA and Ebbutt AF. Trials to assess equivalence: the importance of rigorous methods. BMJ 1996, 313:36-39.

Equivalence trials examples: The Antenatal Care Trial

(Refs: Villar et al, Lancet 2001)

Outcome	New Model	Standard model	OR (95% CI)
LWB(<2500g)	886/11534(7.7%)	788/11040(7.1)	1.10 (0.95-1.27)
Pre-ec/Ec	197/11672(1.7%)	153/11121(1.4%)	1.22 (0.92-1.60)

Equivalence trials examples: The Antenatal Care Trial

(Refs: Villar et al, Lancet 2001)

Conclusion:

- Provision of routine antenatal care by the new model seems not to affect maternal and perinatal outcomes
- It could be implemented without major resistance from women and providers and may reduce cost

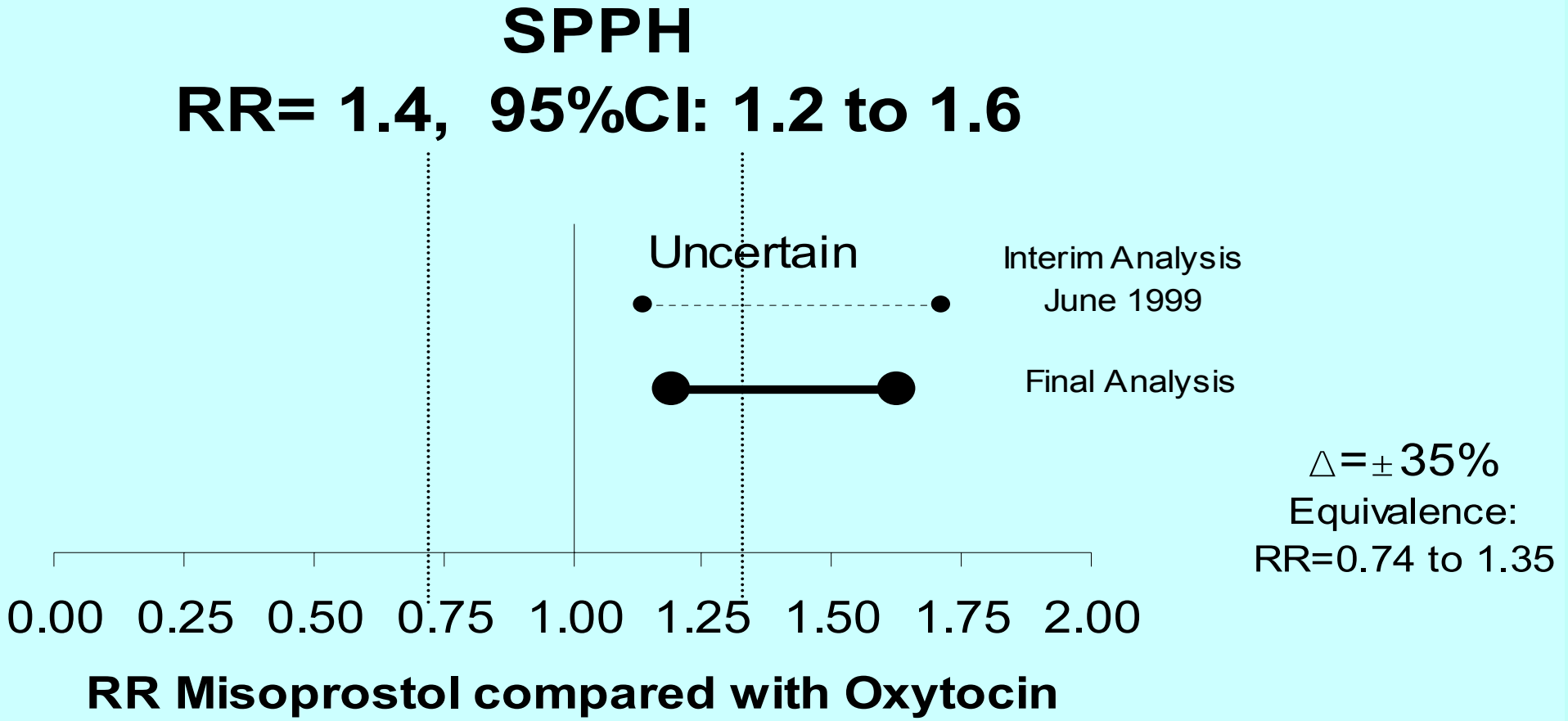
Equivalence trials examples: Prostaglandins for prevention of postpartum haemorrhage

(Ref: Gülmezoglu et al, Lancet 2001)

Outcome	Misoprostol	Oxytocin	RR (95% CI)
Blood loss			
≥ **1000 ml**	366/9214**(4%)**	263/9228**(3%)**	**1.39** (1.19 to 1.63)
Additional uterotonics	1398/9225**(15%)**	1002/9228**(11%)**	**1.40** (1.29 to 1.51)

Equivalence trials examples: Prostaglandins for prevention of postpartum haemorrhage

(Ref: Gülmezoglu et al, Lancet 2001)



Equivalence trials (contd.)

When conclusion regarding equivalence is uncertain:

- If difference is significant (superiority hypothesis): possible to conclude superiority (or inferiority)
- If difference is not significant (superiority hypothesis): inconclusive

Equivalence trials examples: Prostaglandins for prevention of postpartum haemorrhage

(Ref: Gülmezoglu et al, Lancet 2001)

Conclusion:

- 10 IU oxytocin is preferable to 600 mcg oral misoprostol in the active management of third stage of labour