

London School of Hygiene and Tropical Medicine

## PLANNING OF INVESTIGATIONS

D.R. Cox

david.cox@nuffield.ox.ac.uk

## LECTURE 2

- Formulation of questions
- Study design
- Measurement issues
- Analysis
- Interpretation

- Units of study
  - Intrinsic variables
  - Explanatory variables
  - Outcomes
- 
- Cross-sectional studies
  - Prospective studies
  - Retrospective studies
  - Experiments

## 1. Some general considerations (ctd)

- Time scale of investigation
- Metrology
- Previous experience in the field
- Possible interpretations of potential patterns of response
- Generalizability and specificity

## 1. Some general considerations (ctd)

- Time scale of investigation
- Metrology
- Previous experience in the field
- Possible interpretations of potential patterns of response
- Generalizability and specificity
  1. Underlying science
  2. Stability: absence of important interaction

## 1. Some general considerations (ctd)

- Time scale of investigation
- Metrology
- Previous experience in the field
- Possible interpretations of potential patterns of response
- Generalizability and specificity
  1. Underlying science
  2. Stability: absence of important interaction
  3. Assimilation of different kinds of evidence (Cornfield et al, 1959)

## 1. Some general considerations (ctd)

- Time scale of investigation
- Metrology
- Previous experience in the field
- Possible interpretations of potential patterns of response
- Generalizability and specificity
  1. Underlying science
  2. Stability: absence of important interaction
  3. Assimilation of different kinds of evidence (Cornfield et al, 1959)
  4. Appropriate sampling (rarely)



## 1. Some general considerations (ctd)

- Time scale of investigation
- Metrology
- Previous experience in the field
- Possible interpretations of potential patterns of response
- Generalizability and specificity
  1. Underlying science
  2. Stability: absence of important interaction
  3. Assimilation of different kinds of evidence (Cornfield et al, 1959)
  4. Appropriate sampling (rarely)

## 2. Review of general terminology

- Units of study
  1. Smallest subdivision such that two units might have different exposures

## 2. Review of general terminology

- Units of study
  1. Smallest subdivision such that two units might have different exposures
  2. Split levels possible

## 2. Review of general terminology

- Units of study

1. Smallest subdivision such that two units might have different exposures
2. Split levels possible
3. No dependence on exposure to other units

## 2. Review of general terminology

- Units of study
  1. Smallest subdivision such that two units might have different exposures
  2. Split levels possible
  3. No dependence on exposure to other units
  4. Investigation in multiple periods; two types of interdependence
- Is representiveness an issue?

## 2. Review of general terminology

- Units of study
  1. Smallest subdivision such that two units might have different exposures
  2. Split levels possible
  3. No dependence on exposure to other units
  4. Investigation in multiple periods; two types of interdependence
- Is representiveness an issue?
- *Drosophila*; British doctors study; bovine TB; twins

## 2. Review of general terminology

- Units of study
  1. Smallest subdivision such that two units might have different exposures
  2. Split levels possible
  3. No dependence on exposure to other units
  4. Investigation in multiple periods; two types of interdependence
- Is representiveness an issue?
- *Drosophila*; British doctors study; bovine TB; twins
- Role of optimality

- Intrinsic variables

1. Features to be regarded as fixed in the context



- Intrinsic variables

1. Features to be regarded as fixed in the context

- Exposures (treatments)
  1. Role of passage of time
  2. Crucial to objective
  3. Might have been different for each unit from those observed

- Exposures (treatments)
  1. Role of passage of time
  2. Crucial to objective
  3. Might have been different for each unit from those observed
- Outcomes (responses)
  1. Surrogate and intermediate outcomes

- Effect stability
- Main effect principle

- Effect stability
- Main effect principle
  1. Finding an interaction is not a conclusion

- Effect stability
- Main effect principle
  1. Finding an interaction is not a conclusion
- Types of statistical interaction
  1. Exposure by exposure interaction
  2. Exposure by intrinsic feature interaction

- Effect stability
- Main effect principle
  1. Finding an interaction is not a conclusion
- Types of statistical interaction
  1. Exposure by exposure interaction
  2. Exposure by intrinsic feature interaction
  3. Relevance for observational studies; temporal issues

### 3. Implementation criteria

- Avoidance of systematic error



### 3. Implementation criteria

- Avoidance of systematic error
  1. Enforced balance on intrinsic features
  2. Measurement of competing sources
  3. Randomization

### 3. Implementation criteria

- Avoidance of systematic error
  1. Enforced balance on intrinsic features
  2. Measurement of competing sources
  3. Randomization
- Control of random error

### 3. Implementation criteria

- Avoidance of systematic error
  1. Enforced balance on intrinsic features
  2. Measurement of competing sources
  3. Randomization
- Control of random error
- Appropriate scale of effort
  1. How should this be formulated?

### 3. Implementation criteria

- Avoidance of systematic error
  1. Enforced balance on intrinsic features
  2. Measurement of competing sources
  3. Randomization
- Control of random error
- Appropriate scale of effort
  1. How should this be formulated?
  2. Decision theory

### 3. Implementation criteria

- Avoidance of systematic error
  1. Enforced balance on intrinsic features
  2. Measurement of competing sources
  3. Randomization
- Control of random error
- Appropriate scale of effort
  1. How should this be formulated?
  2. Decision theory
  3. Width of confidence interval: standard error of estimate

### 3. Implementation criteria

- Avoidance of systematic error
  1. Enforced balance on intrinsic features
  2. Measurement of competing sources
  3. Randomization
- Control of random error
- Appropriate scale of effort
  1. How should this be formulated?
  2. Decision theory
  3. Width of confidence interval: standard error of estimate
  4. Power

### 3. Implementation criteria

- Avoidance of systematic error
  1. Enforced balance on intrinsic features
  2. Measurement of competing sources
  3. Randomization
- Control of random error
- Appropriate scale of effort
  1. How should this be formulated?
  2. Decision theory
  3. Width of confidence interval: standard error of estimate
  4. Power
  5. Inverse question

### 3. Implementation criteria

- Avoidance of systematic error
  1. Enforced balance on intrinsic features
  2. Measurement of competing sources
  3. Randomization
- Control of random error
- Appropriate scale of effort
  1. How should this be formulated?
  2. Decision theory
  3. Width of confidence interval: standard error of estimate
  4. Power
  5. Inverse question
  6. Possibilities of differential replication



### 3. Implementation criteria

- Avoidance of systematic error
  1. Enforced balance on intrinsic features
  2. Measurement of competing sources
  3. Randomization
- Control of random error
- Appropriate scale of effort
  1. How should this be formulated?
  2. Decision theory
  3. Width of confidence interval: standard error of estimate
  4. Power
  5. Inverse question
  6. Possibilities of differential replication
  7. Square root rule

### 3. Implementation criteria

- Avoidance of systematic error
  1. Enforced balance on intrinsic features
  2. Measurement of competing sources
  3. Randomization
- Control of random error
- Appropriate scale of effort
  1. How should this be formulated?
  2. Decision theory
  3. Width of confidence interval: standard error of estimate
  4. Power
  5. Inverse question
  6. Possibilities of differential replication
  7. Square root rule

- Multiplicity of questions (factorial principle)

- Multiplicity of questions (factorial principle)
- Rahman et al (*New Eng. J. Med.* **365** (2011),518-526.)
  1. Study to compare two treatments for pleural infection; t-PA and DNase.
  2. Four groups of nearly equal size, Double placebo, t-PA plus placebo, placebo plus DNase, both t-PA and DNase
  3. Strong interaction; double treatment effective, single treatment not
- Intermediate assessment and modification

- Multiplicity of questions (factorial principle)
- Rahman et al (*New Eng. J. Med.* **365** (2011),518-526.)
  1. Study to compare two treatments for pleural infection; t-PA and DNase.
  2. Four groups of nearly equal size, Double placebo, t-PA plus placebo, placebo plus DNase, both t-PA and DNase
  3. Strong interaction; double treatment effective, single treatment not
- Intermediate assessment and modification
- Ability to detect and explain the unanticipated

- Multiplicity of questions (factorial principle)
- Rahman et al (*New Eng. J. Med.* **365** (2011),518-526.)
  1. Study to compare two treatments for pleural infection; t-PA and DNase.
  2. Four groups of nearly equal size, Double placebo, t-PA plus placebo, placebo plus DNase, both t-PA and DNase
  3. Strong interaction; double treatment effective, single treatment not
- Intermediate assessment and modification
- Ability to detect and explain the unanticipated
- Advantages of multiple approaches
- R.A.Fisher's dictum; Cornfield et al (1959)