

London School of Hygiene and Tropical Medicine

PLANNING OF INVESTIGATIONS

D.R. Cox

david.cox@nuffield.ox.ac.uk

1. Preliminary comments

Convenient to separate design, analysis and interpretation, although part of good design is to ensure that incisive analysis will be possible.

Important to check that analysis of key questions will be feasible.

But complete specification of analysis in advance unwise.

2. Initial formulation

Formulation of questions

2. Initial formulation

Formulation of questions

- Units of study
- Intrinsic features
- Exposures
- Outcome

2. Initial formulation

Formulation of questions

- Units of study
- Intrinsic features
- Exposures
- Outcome

Phases

- Design
- Measurement issues
- Data collection
- Analysis
- Interpretation

3. Types of study

- Descriptive cross-sectional study (possibly repeated)

3. Types of study

- Descriptive cross-sectional study (possibly repeated)
 1. Not everything has to be measured every time on every study individual

3. Types of study

- Descriptive cross-sectional study (possibly repeated)
 1. Not everything has to be measured every time on every study individual
- Analytic cross-sectional study

3. Types of study

- Descriptive cross-sectional study (possibly repeated)
 1. Not everything has to be measured every time on every study individual
- Analytic cross-sectional study

German study of Type 2 diabetes

- At single clinic visit, glucose control, and psychometric score of disease knowledge and attribution
- Years since diagnosis, educational status

- Prospective (cohort) study

- Prospective (cohort) study

1. British male doctors 50 year study: Doll, Peto and Sutherland (2004)

- Prospective (cohort) study

1. British male doctors 50 year study: Doll, Peto and Sutherland (2004)
2. Framingham study

- Prospective (cohort) study
 1. British male doctors 50 year study: Doll, Peto and Sutherland (2004)
 2. Framingham study
- Retrospective (case-control) study

- Prospective (cohort) study
 1. British male doctors 50 year study: Doll, Peto and Sutherland (2004)
 2. Framingham study
- Retrospective (case-control) study
 1. Doll and Bradford Hill (1950)

- Prospective (cohort) study
 1. British male doctors 50 year study: Doll, Peto and Sutherland (2004)
 2. Framingham study
- Retrospective (case-control) study
 1. Doll and Bradford Hill (1950)
 2. All patients with carcinoma of lung at 20 London hospitals over a 18 month period
 - Control patient at same hospital, same age band and gender
 - Interviewed by one of four almoners
 - After some exclusions roughly 700 patients in each group
 - Careful study of possible biases
- Experiment (intervention, usually but not necessarily randomized)

- Prospective (cohort) study
 1. British male doctors 50 year study: Doll, Peto and Sutherland (2004)
 2. Framingham study
- Retrospective (case-control) study
 1. Doll and Bradford Hill (1950)
 2. All patients with carcinoma of lung at 20 London hospitals over a 18 month period
 - Control patient at same hospital, same age band and gender
 - Interviewed by one of four almoners
 - After some exclusions roughly 700 patients in each group
 - Careful study of possible biases
- Experiment (intervention, usually but not necessarily randomized)
- Mixtures of types
- Other possibilities

4. Broad objectives

- Avoid systematic distortion

4. Broad objectives

- Avoid systematic distortion
- Avoid systematic distortion; Lanarkshire milk experiment (Student, 1931)

4. Broad objectives

- Avoid systematic distortion
- Avoid systematic distortion; Lanarkshire milk experiment (Student, 1931)
- Control of random error

4. Broad objectives

- Avoid systematic distortion
- Avoid systematic distortion; Lanarkshire milk experiment (Student, 1931)
- Control of random error
- Appropriate scale of effort

4. Broad objectives

- Avoid systematic distortion
- Avoid systematic distortion; Lanarkshire milk experiment (Student, 1931)
- Control of random error
- Appropriate scale of effort
- Factorial principle

5. The purposes of measurement

- intrinsic variables
- exposures
- outcomes

5. The purposes of measurement

- intrinsic variables
- exposures
- outcomes

Purpose of intrinsic variables

- to control unwanted sources of variability
- to check for stability of exposure effects
- to improve generalizability

Aspects of exposures

- factorial principle
- role of interactions

6. Some broader aspects

- Time scale of investigation

6. Some broader aspects

- Time scale of investigation
- Metrology

6. Some broader aspects

- Time scale of investigation
- Metrology
 1. Chromatography

6. Some broader aspects

- Time scale of investigation
- Metrology
 1. Chromatography
 2. Pain, quality of life, etc

6. Some broader aspects

- Time scale of investigation
- Metrology
 1. Chromatography
 2. Pain, quality of life, etc
 3. Issues of dimensionality

6. Some broader aspects

- Time scale of investigation
- Metrology
 1. Chromatography
 2. Pain, quality of life, etc
 3. Issues of dimensionality
 4. Possibility of development within a new study

6. Some broader aspects

- Time scale of investigation
- Metrology
 1. Chromatography
 2. Pain, quality of life, etc
 3. Issues of dimensionality
 4. Possibility of development within a new study
- Previous experience in the field

6. Some broader aspects

- Time scale of investigation
- Metrology
 1. Chromatography
 2. Pain, quality of life, etc
 3. Issues of dimensionality
 4. Possibility of development within a new study
- Previous experience in the field
 1. Deadhand of precedent

6. Some broader aspects

- Time scale of investigation
- Metrology
 1. Chromatography
 2. Pain, quality of life, etc
 3. Issues of dimensionality
 4. Possibility of development within a new study
- Previous experience in the field
 1. Deadhand of precedent
- Possible interpretations of potential patterns of response

6. Some broader aspects

- Time scale of investigation
- Metrology
 1. Chromatography
 2. Pain, quality of life, etc
 3. Issues of dimensionality
 4. Possibility of development within a new study
- Previous experience in the field
 1. Deadhand of precedent
- Possible interpretations of potential patterns of response
 1. Prospective and retrospective
 2. Independent check on retrospective explanations

A veterinary example

Three treatments, 10 replicates:

Units of study; 30 10km radius “circles” grouped in sets of 3

A veterinary example

Three treatments, 10 replicates:

Units of study; 30 10km radius “circles” grouped in sets of 3

Exposures

- Control, survey only
- Localized culling of wildlife after detection of disease in cattle
- Large scale culling annually of large area

Outcome: farm breakdown rate over 5 year period

A veterinary example

Three treatments, 10 replicates:

Units of study; 30 10km radius “circles” grouped in sets of 3

Exposures

- Control, survey only
- Localized culling of wildlife after detection of disease in cattle
- Large scale culling annually of large area

Outcome: farm breakdown rate over 5 year period

Anticipated pattern of response

Actual pattern on intermediate analysis

Interpretation

Bait-marking trial

SPECIFIC REFERENCES

- Cornfield, J. and 5 others (2009). Smoking and lung cancer: recent evidence and discussion of some questions. *Int. J. of Epidemiology* **38**, 1175-1191. Reproduced with discussion from 1959 paper in *J. Nat. Cancer Inst.* [Synthesis of evidence]
- Cox, D.R. and 5 others (1992). Quality of life assessment: can we keep it simple?. *J.R. Statist. Soc. A* **155**, 353-393. [Metrology]
- Cox, D.R. and Wermuth, N. (1996). *Multivariate dependencies*. London: Chapman and Hall. [Diabetic example]
- Doll, R. and Hill, A.B. (1950). Smoking and carcinoma of the lung. *Brit. Med. J.* **2**, 739-748. [Case-control study, example]
- Doll, R., Peto, R., Boreham, J. and Sutherland, I. (2004). Mortality in relation to smoking. 50 years observation on male British doctors. *Brit. Med. J.* **328**, 819. [Cohort study, example]
- Donnelly, C.A. and 13 others (2006). Positive and negative effects of widespread badger culling on tuberculosis in cattle. *Nature* **439**, 843-846. [Bovine TB]

'Student' (1931). The Lanarkshire milk experiment. *Biometrika* **23**, 398-406. [Systematic error]

Woodroffe, R. and 8 others (2006). Effects of culling on badger *Meles meles* spatial organization and implications for control of the disease. *J. Applied Ecology* **43**, 1-10. [Bovine TB]

GENERAL REFERENCES

- Breslow, N.E. and Day, N. (1980). *Statistical methods in cancer research, vol.1, The analysis of case-control studies*. Lyon: IARC.
- Breslow, N.E. and Day, N. (1983). *Statistical methods in cancer research, vol.2, The analysis of case-cohort studies*. Lyon: IARC.
- Cox, D.R. (1958). *Planning of experiments*. New York: Wiley.
- Cox, D.R. and Donnelly, C.A. (2012). *Principles of applied statistics*. Cambridge University Press.
- Fisher, R.A. (1935). *Design of experiments*. Edinburgh: Oliver and Boyd, and subsequent editions.
- Keogh, R.H. and Cox, D.R. (2014). *Case-control studies*. Cambridge University Press.
- Rosenbaum, P.R. (2010). *Design of observational studies*. New York: Springer.
- Thompson, S.K. (1992). *Sampling*. New York: Wiley.