Association of Veterinary Anaesthetists

Newmarket 2005

Association of Veterinary Anaesthetists

Residents' Training Day

24th September 2005

Animal Health Trust

2 A practical approach to the planning, design and analysis of clinical studies

V. Adams

Epidemiology Unit, Centre for Preventive Medicine, Animal Health Trust, Lanwades Park, Kentford, Newmarket, Suffolk CB8 7UU, UK

Outline

Part I: Essentials of clinical epidemiology
- Introduction
- Study design

Part II: Data management and analysis
- Data collection
- Data entry
- Data management
- Data analysis

Part I

Clinical epidemiology

- Defining research question
- Sampling issues
- Types of studies
  - quality of evidence
  - internal and external validity
- Types of data and variables
- Outcome measures
- Bias
- Chance and probability
- Sample size calculations
- Diagnostic test evaluation
- Statistics
  - looking at data
  - descriptive statistics
  - normal distribution
  - probability
  - inferential statistics
  - presenting results

Epidemiology is ...

"The study of the distribution and determinants of health-related states or events in specified populations, and the application of this study to the control of health problems."

J. Last 1995

"Study of the health status of populations." *B. Toma et al. 1999*

a continuum ...

Demography	Survey research	Experimental medicine

With a focus on groups of subjects rather than individuals.

Chemistry – quintessential experimental discipline, isolated systems with rigorous control over external factors.

Epidemiology – observes the natural world, controls nothing and uses statistics to analyse the observations.

What is clinical epidemiology?

What it isn't ...

- 'Classical' epidemiology
- Pure statistics/statistical theory
- Pure clinical perspective – care of individual patients

'Classical' epidemiology

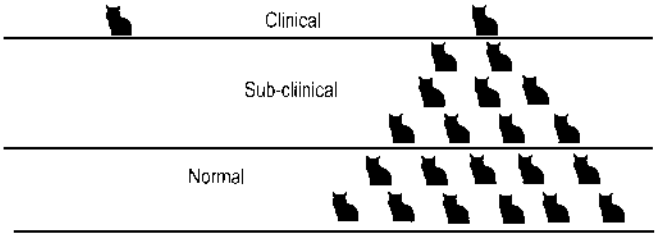
- Surveillance
- Epidemic investigation and control
  - Infectious disease epidemiology
  - Outbreak investigation
- Natural history of disease

W5

- Description of patterns of occurrence of health-related states or events in groups
  - answering the questions of 'who?', 'what?' 'where?', and 'when?'
- studies of groups to evaluate potential associations between risk factors and health outcomes
  - to answer the question 'why?'

Iceberg phenomenon of disease

Clinical perception of problem Actual 'herd' problem



Statistics

- A branch of mathematics and probability theory that is used to sample, analyse, and infer from data.
- Data = a collection of items of information.
- The singular of data is *datum*, not anecdote!

Statisticians

- ... contribute to and advance the basic discipline and theory of statistics.
- ... do statistics.
- ... help other researchers with their statistics.

Clinical epidemiology is ...

- 'clinical' – seeks to answer clinical questions and to guide clinical decision making.
- 'epidemiology' – the care of individual patients in the context of the larger population and methods used to answer questions.
- Quality of clinical information and its correct interpretation
  - Understanding strengths and weaknesses of clinical evidence.
  - Perspective on the extent to which clinical efforts determine health outcomes.
- Purpose: to foster methods of clinical observation and interpretation that lead to valid conclusions.

Hippocrates, 400 BC

- On airs, waters and places ...
  - Hippocrates advised physicians to be aware of the environment and its effects on illness and well-being.
  - He recognised that regions differ in terms of their temperature, humidity and openess to winds which he felt influenced the health of people.
- Evidence-based medicine
  - An approach to practice in which the clinician is aware of the evidence in support of their clinical practice and the strength of that evidence.

Clinical epidemiology is a methodology to obtain evidence that clinical outcomes ...

Frequency... occur at calculable frequencies
Cause... are due to certain predisposing 'risk' factors
Diagnosis... can be diagnosed with certain tests
Treatment... can be improved by certain treatments
Prognosis... may lead to certain consequences, or
Prevention ... can be prevented by certain interventions.

Clinical questions

Abnormality	Is the patient sick or well?
Frequency	How often does this disease occur?

Cause	What conditions lead to this disease?
Risk	What factors are associated with an increased risk of disease?
Diagnosis	How accurate and useful are tests used to diagnose this disease?
Treatment	How does treatment change the course of this disease?
Prognosis	How effective is Tx A?
Prevention	What are the consequences of having this disease?

Where an epidemiologist can help

- Before data collection
  - At the planning stage
    - Asking an answerable question
  - With the study design
    - Type of study, outcome measures, questionnaires
  - At the grant proposal stage
    - Sample size calculations, planned analysis
- Data management
  - Spreadsheets, databases, questionnaires
- With the analysis
  - Descriptive and inferential statistics

Study design

- What questions are to be answered?
  - Clear objectives
    - SMART
      - Specific, Measureable, Achievable, Relevant, Timely
  - Testable hypotheses
  - Simplicity of design
  - Asking an answerable question
    - Avoiding a type III error

Study design

FINER:

Feasible

Interesting

Novel

Ethical

Relevant

Feasible

Subjects

Expertise

Cost

Scope

Interesting

To the investigator

To those who fund research

Novel

Contributing new information

Confirms or refutes previous findings

Extends previous findings

Provides new findings

Ethical

To the investigator

To those who fund research

Relevant

To scientific knowledge

To clinical practice

To future research directions

Defining the research question

- Research question = objective of the study or the uncertainty that the investigator wants to resolve.
- Process
  - often begins with a general concern.
  - must be narrowed down to a concrete, researchable issue.
- Difficulty
  - Finding an important question that can be transformed into a feasible and valid study plan.
  - Asking an answerable question.
- Questions often emerge from the findings and problems observed in prior studies.
  - New approaches to old problems.

Example research question

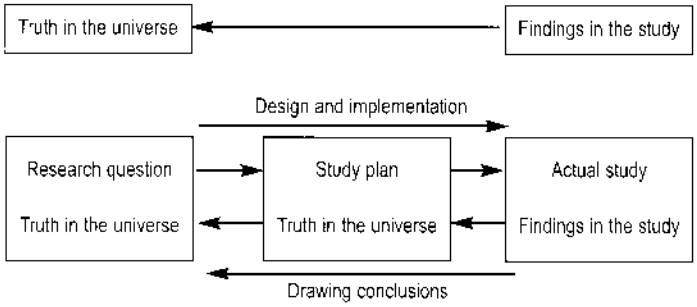
- Initial question:
  - What degree of hypothermia occurs during general anaesthesia?
- More specific questions:

- How frequently does hypothermia occur?
- How long does it take for a dog to become hypothermic?
- Can we take measures to prevent hypothermia?

- More specific question:
  - Does using external methods reduce the occurrence of hypothermia during general anaesthesia for radiology?
- Even more specific:
  - Does using HME and/or a Bair Hugger reduce the occurrence and severity of hypothermia during general anaesthesia for radiology?
- Research design:
  - A randomised clinical trial of two methods of reducing hypothermia during general anaesthesia.
- Hypothesis:
  - The severity and degree of hypothermia during G/A will be reduced through the use of HME or HME + Bair Hugger compared with a control group with no intervention.

Sampling strategy

- Populations
  - General population
  - Target population
- Sample population



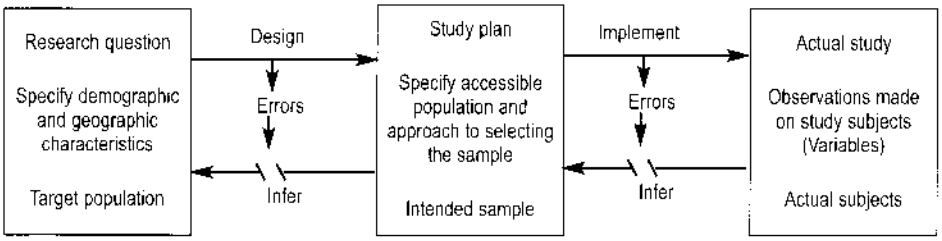
Beginning with a decision about what problem one wishes to investigate, a study is then undertaken to answer the research question.

This involves 2 steps:

1) the first step is to design a study plan with subjects and measurements chosen to enhance the process of appropriately answering the research question with a goal of being able to generalise the conclusions to the animals and phenomena (or problem) addressed by the research question;

2) the second step is to carry out the study in such a way as to enhance the likelihood of getting the right answer, that is, to draw conclusions about what actually happened in the study.

Sampling issues

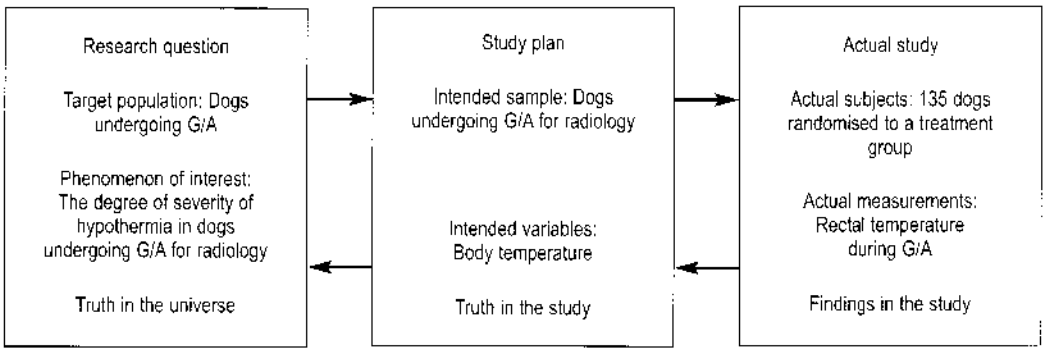


If the intended sample and variables do not represent the target population and phenomena of interest, design errors may distort inferences about the answer to the research question.

If the actual subjects and measurements do not represent the intended sample and variables, implementation errors may distort inferences about what actually happened in the study.

No study is free of errors and inferences are never perfectly valid. The goal is to maximise the validity of drawing inferences from what happened in the study sample to reach conclusions about the nature of things in the population.

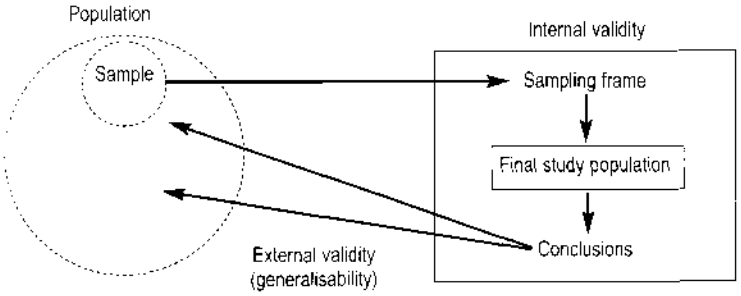
Example



Sampling and study design

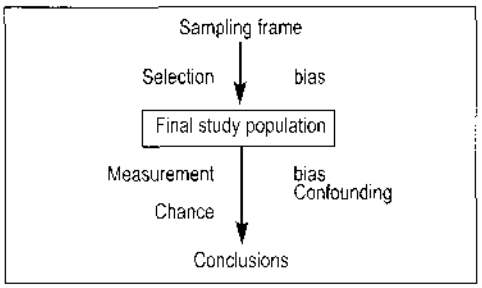
- Research question
  - → Sampling strategy
    - Target population → Sample
  - → Study design

Internal and external validity

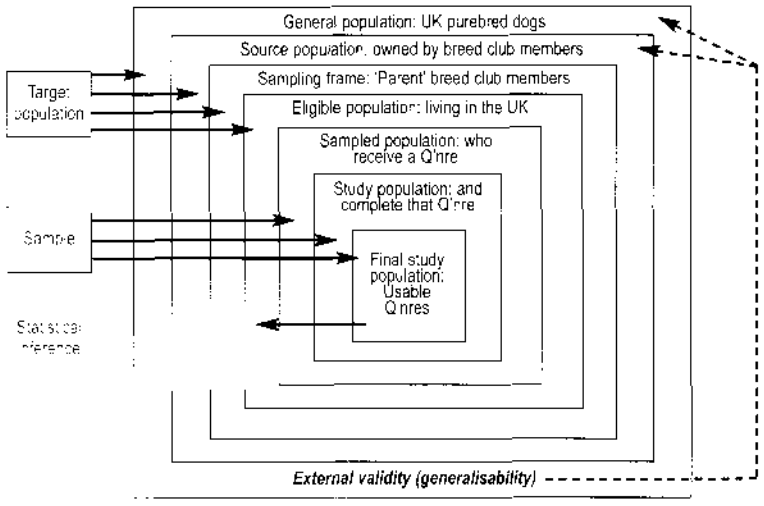


The sampling frame or sampling base is the assemblage of individuals or groups on which sampling is performed. A sample is the subset of a population selected for inclusion in a study. A collection of sample units or subjects derived from a sampling frame.

Internal validity



Internal validity is the degree to which the results of the study are correct for the sample of patients being studied. It is internal because it applies to the conditions of the particular group of patients being observed and not necessarily to others. It is determined by how well the design, data collection, and analyses are carried out and may be affected by bias, leading to totally erroneous conclusions.



The sampling strategy or approach or design is the detailed description of the selection process used to obtain a sample from a population.

The general or reference population is the exhaustive population for which we want to extrapolate conclusions from a study. This will be the target population if it includes all accessible and inaccessible individuals.

The source or underlying population is that fraction of the general population from which the sampling frame comes from.

The sampling frame or base is the assemblage of individuals or groups on which sampling is performed.

The eligible population is that fraction of the source population possessing the inclusion criteria

The sampled population is that fraction of the eligible population that is effectively retained in the sample after application of a sampling procedure –those that receive a questionnaire.

The study population is that part of the sample that effectively undergoes observation, after applying exclusion criteria – in this case breed club members living overseas and losing those that refuse to participate.

The final study population is that fraction of the sample that underwent the application of the study protocol and on which observations were effectively collected. It is what is left of the sampled population after exclusion of all cases that have been rejected or lost to follow-up throughout the study.

The sample is defined as the subset of a population selected for inclusion in a study. Depending on the response rate, this may be one of any of the 3 interior boxes.

The target population, as the population to which we would like to apply or extrapolate the results of the study to, may be any one of the outer 4 boxes.

Statistical inference is the act or process of reaching a conclusion from observations that are considered valid, and this requires that certain assumptions be satisfied in order for the conclusion to be valid. Using statistics, inference is the development of generalization from sample data with a calculated uncertainty.

External validity or generalisability is the degree to which the results of a study hold true in other populations (in other settings such as other times or places), assuming that internal validity has been confirmed. For an individual clinician, it is an answer to the question: "assuming that the results of this study are true, do they apply to my patient as well?". Whether the results of a study are generalisable depends on the extent to which the surveyed population is representative of the target population. Generalizability expresses the validity of assuming that patients in a study are comparable with other patients. Consideration must be given to the risk that conclusions may only be valid for the population under study.

Statistics - the role of chance

Observations about disease are made on a sample of patients rather than all those with the disease in question.

These observations may misrepresent the situation in the population as a whole because of chance.

The divergence of an observation on a sample from the true population value, due to chance alone, is called random variation.

Type I error

- Type I error: occurs when a false-positive conclusion is made that there is a treatment effect or association when there is not.
  - α = alpha = the risk of making a Type I error before the study begins.
  - α becomes the P value as the probability of a false-positive conclusion.

Type II error

- Type II: error occurs when a false-negative conclusion is made that there is no treatment effect or association when there truly is.
  - ß = beta = the risk of drawing a false-negative conclusion.
  - 1 - ß = power of a study = the probability of drawing a true-positive conclusion when you ought to.
- Statistics are used to estimate the probability of chance (random variation) accounting for clinical results.
- A knowledge of statistics helps reduce the probability of chance alone accounting for the observed results
  - by allowing one to plan the study design and analysis (more on this to come).

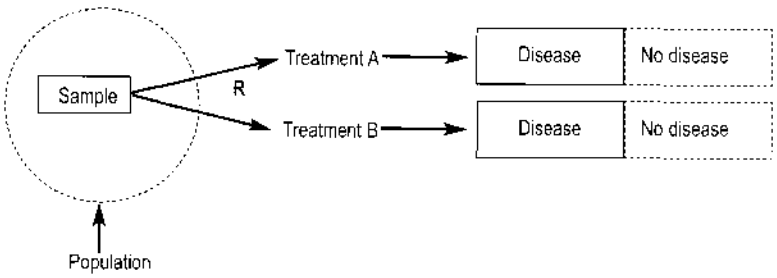
Types of studies

1. ***Experimental (interventional) designs***
   - Observation of the effects of an intervention on study subjects.
2. ***Observational designs***
   - Observation of events in study subjects.
     - Descriptive
     - Analytic

1. Experimental designs

Randomised controlled clinical trial (RCT):

- Two groups are created by random allocation of the treatments to eligible subjects.
  - Followed to observe effect of treatments on disease.
    - Groups are compared to evaluate the efficacy of treatment.

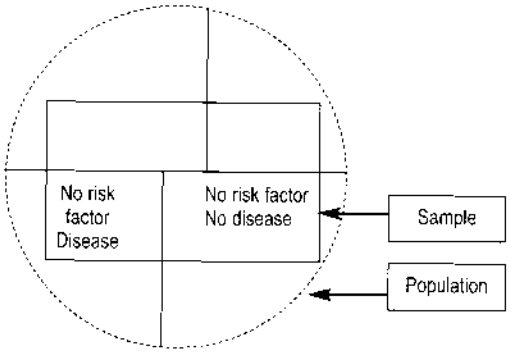


2. Observational designs

- Descriptive
  - Data-gathering, surveillance, disease detection, and prevalence surveys.
    - Proportions or rates of disease
      - Prevalence, incidence
      - (with confidence intervals)
    - Measures of central tendency and dispersion

Cross-sectional (prevalence) study

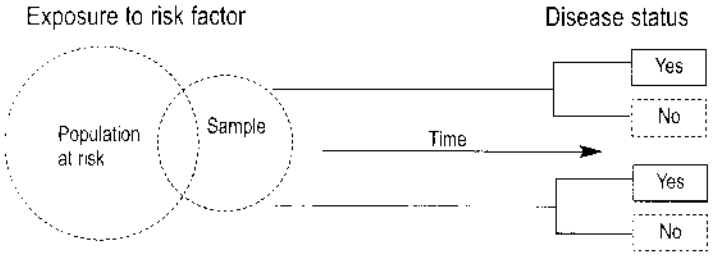
- One group is examined at one point in time.
  - Exposure and disease are measured at the same time.
    - Observing the prevalence of disease among those exposed and unexposed to a risk factor.



- Analytic
  - Statistical inferences about disease occurrence and possible causal associations.
    - Statistical tests of significance, risk factor analysis, survival analysis, multiple regression, mathematical modelling, simulation, etc.
      - To compare groups and reach conclusions.

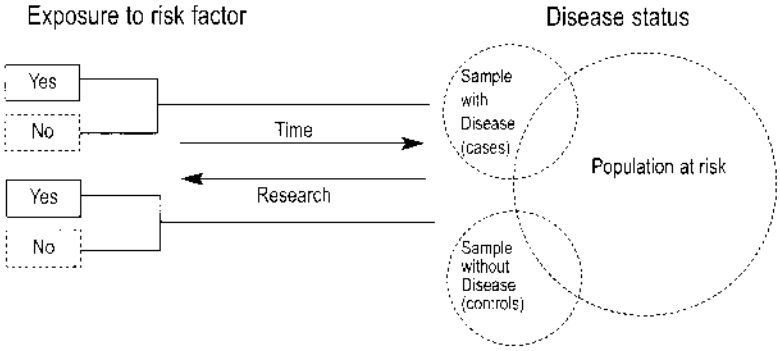
Cohort study

- A group followed over time.
  - Exposed and non-exposed groups.
    - Observe and compare incidence of disease.
      - Calculate level of risk of developing disease in relation to exposure (hypothesised risk factor).



Case-control study

- Two groups based on presence/absence of disease.
  - Information obtained on potential risk factors and exposures.
    - Diseased and non-diseased groups compared.



Matching study design to research question

Question	*Design*
Diagnosis	Cross-sectional
Prevalence	Cross-sectional
Incidence	Cohort
Cause or Risk	Cohort or Case-control
Prognosis	Cohort
Treatment or Prevention	Clinical trial

Quality of evidence

Increasing quality of evidence ↑

- Meta-analysis/systematic review
- Randomised clinical trial
- Non-randomised clinical trial
- Cohort study
- Case-control study
- Cross-sectional study
- Case series/Case report
- Expert opinion

"Epidemiology is much more than finely dressed statistics. It is a scientific discipline with roots in biology, logic, and the philosophy of science."

K. Rothman 2002

Epidemiology and anaesthesia

D. Brodbelt

Lecturer in Veterinary Anaesthesia, Royal Veterinary College, Hawkshead Lane, North Mymms, Hatfield, Hertfordshire AL9 7TA, UK

Epidemiology has been defined as the "...study of the distribution and determinants of disease frequency..." (Hennekens and Buring 1987). If the anaesthetic outcome of interest, eg anaesthetic mortality or intraoperative patient blood pressure, is substituted for 'disease' in the above definition then epidemiology becomes relevant to anaesthesia. The application of different epidemiological methods can thus be applied to anaesthesia as for any subject. This presentation will focus on the different study designs and their relevance to anaesthesia and the relationship between associations observed and causation.

The basic design strategy used depends on whether the investigation focuses on describing the distributions of disease, ie descriptive studies or understanding the factors contributing to disease ('the determinants'), ie analytical studies.

Descriptive studies

1. Correlational studies

Data coming from entire populations are used to compare disease frequencies between different groups during the same time period or the same group during different time points; eg study comparing the risk of anaesthetic morbidity in a population at different time points.

Advantages:

Often inexpensive, relatively easy to undertake

Useful for formulating hypotheses to then test

Disadvantages:

Data only at population level, not the individual and hence can not link exposure (e.g. to a specific anaesthetic drug) to outcome in the same individual.

Can not control for confounding factors.

2. Case reports and case series

Detailed reports on a single individual or series of individuals; eg report on a horse (or series of horses) developing pulmonary oedema after anaesthesia.

Advantages:

Identify hypotheses for further study

Disadvantages:

Can not test proposed explanation or hypothesis

3. Cross-sectional surveys

The exposure status of an individual and the outcome of interest is assessed at the same time point; eg study of individual veterinarian's use of analgesics

Advantages:

Generate a hypothesis about an association

Generate prevalence data

Disadvantages:

Can not always distinguish whether exposure proceeded outcome or occurred as a result of the outcome. Generally, they can not be used to test an association, though for factors that remain unaltered over time (e.g. sex, breed, race etc) the cross sectional study can provide evidence for a statistical association.

Analytical studies

1. Observational studies

The investigator observes the course of events, without influencing the events, and records the individuals exposed and not exposed to a given factor and those that develop the outcome of interest.

a) Case - control studies – A group of patients with a given outcome are identified (Cases) and then compared to a group without the disease or outcome of interest (Controls) for their exposure histories.

eg risk factors for anaesthetic death – Compare Cases (deaths) to controls (non-death) for risk factors (Brodbelt, Brearley *et al.* 2005).

eg 2 Risk factors for oesophageal stricture formation (Case = oesophageal stricture, control = no stricture, look for risk factors).

Advantages:

Efficient for rare outcomes and multiple exposures

Good for diseases of long latency

Cost efficient

Disadvantages:

Inefficient for rare exposures

Susceptible to bias

Selection bias – differential selection of either cases or controls based on exposure status. Selection of controls often difficult.

Recall bias – differential recall of exposure based on outcome.

Cannot calculate incidence directly.

Temporal relationship between exposure and outcome may be difficult to establish

b) Cohort studies – Subjects are classified based on their exposure to a given factor and then followed for a specified period of time and their outcome status is recorded.

eg Risk factors for anaesthetic death – note exposure (e.g drugs used) follow group of patients. and record outcome (Johnston *et al.* 1995; Dyson *et al.* 1998; Johnston *et al.* 2002).

eg 2 Risk factors for perioperative morbidity

Advantages:

Good for rare exposures, and common outcomes
Temporal sequence of exposure and outcome established
Good for multiple outcomes
Less susceptible to selection bias
Measures incidence

Disadvantages:

Inefficient for rare outcomes
Time-consuming and expensive
Prone to bias due to losses to follow up

2. Intervention studies

Also called a clinical trial. The investigator allocates exposure often randomly and then follows the outcome.

eg trial of isoflurane versus halothane in horses (Eastment *et al.* 2002; Johnston *et al.* 2004).

eg 2 Perioperative opioid analgesia trial/therapeutic trial

Advantages:

Potential for greater validity of results than observational study

Disadvantages:

Ethical issues more of a concern
Observation bias if not blinded study
Cost

Association and causation

Most studies report associations between an exposure and an outcome. In interpreting these results often an implication of causation is made, ie that the factor under study in some way contributed to the outcome. Association does not imply causation and many factors associated with an outcome are not causative. Hill (1965) described a number of criteria against which to assess the likely role of observed factors in the causation of an outcome. The strength of the association, the consistency with other work, the specificity of the association, temporality of the relationship, the presence of a biological gradient, the biological plausibility, the coherence with the known biology of the disease or subject under study, the presence of supporting experimental evidence, and the presence of analogy to a similar condition are all criteria to base an assessment of the likely role of an association in causation (Hill 1965).

Further reading

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Hennekens and Buring (1987) Epidemiology in Medicine

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Association of Veterinary Anaesthetists

V. Adams

Epidemiology Unit, Centre for Preventive Medicine, Animal Health Trust, Lanwades Park, Kentford, Newmarket, Suffolk CB8 7UU, UK

Part II: Data management and analysis

Acknowledgement: Dr H. Townsend, University of Saskatchewan

Data collection

- What data to collect?
  - Not too much
    - limited to that which is required to answer the study objectives and hypotheses
    - collected data must be entered, checked and verified whether or not it is used
    - 'rule of thumb': 10 cases/variable
    - avoid excessive use of matching
    - avoid excessive repeated measures
  - Not too little
    - biologically meaningful potential confounding variables
    - often very difficult if not impossible to go back and get data that you failed to collect
    - missing values may cause big problems in the analysis and subsequent validity of the study
    - cases with missing data will be dropped from any multivariate analysis
- Deciding on the variables to include in the study
  - Careful reflection and cross-checking with hypotheses
  - Consider use of proxy or surrogate measures
    - more easily accessible/measureable
    - useful for hypothesis generation
    - but
  - Review other similar studies
  - Advisory committee, research group meetings and discussions
  - Expert opinion
  - Requirements for study administration and final report
  - Cost benefit analysis to explore relationship between costs and benefits of obtaining data
- Naming variables
  - Short but informative names
    - ~ 8 characters, depends on stats package
  - Keep a master list of variables
    - name, label and short description
      - surv_dx = survival = time from diagnosis to death/censoring in days

- bw = body weight in kg
- maint_ag = maintenance anaesthetic agent (halo/iso/prop)

- What form should the data be in?
  - Consider how the data will be analysed
    - which statistical tests?
    - any statistical modeling?
    - each variable considered for inclusion in the study should be examined with respect to its compatibility with the planned statistical analysis and any software limitations
      - types of variables and data
      - create dummy tables
  - Continuous variables
    - eg age, body weight, T4 level
    - continuous → categorical
  - Categorical variables
    - eg sex, breed, age categories
    - only if not available in the continuous form
    - categorical ↛ continuous
  - Age
    - Record birthdate and date of diagnosis or death
      - Can calculate age at diagnosis or death

C2	= A2+ (B2/12)		
	A	B	C
1	Age_y	age_m	age
2	3	6	3.50
3	1	3	1.25
4	4	9	4.75
5	6	2	6.17
6	2	8	2.67

- Consider how many cases are needed
  - Sample size calculations
    - statistical techniques exist for estimating required sample size
    - but calculations require some idea of the results expected at the end of the study before it has even been conducted!
    - More on this later

Data entry

- Construct dummy tables including all proposed variables
  - Cross-check variables against the study hypotheses and planned statistical analysis for convenience and feasibility
  - Data tables should be consistent with the planned approaches to data analysis
    - to avoid unnecessary data manipulation
    - not necessarily in a format suitable for publication
- Forms/questionnaires
  - Quality and design of forms - direct effect upon the quality of the data
  - Test before using in the study
  - Design
    - layout and headers should be consistent
    - should be professional looking & well laid out
    - facilitated by the use of a database program
  - Consider use of automated data entry systems
- Databases or spreadsheets?
  - Databases – MS Access, Paradox, Epi Info, Oracle
    - facilitate data entry and coding
    - validation tools for data entry
    - link multiple data sheets per animal, multi-centre studies
    - can be used to generate spreadsheet tables or data can be exported for import into statistical software
    - sorting is idiot-proof
    - good for studies with ≥ 100 cases
  - Spreadsheets – Excel, Quattro Pro, Lotus
    - spreadsheets are OK if they follow the same format as databases
    - 'categorical' vs. 'table' formats
      - categorical format preferred
        - cases = rows and variables = columns
    - sorting can be problematic
    - good for studies with ≤ 100 cases
- Data structure
  - Repeated measures on cases
    - cases = rows may represent individual animal or a repeated measure
    - variables = columns
  - Hierarchical or multilevel data
    - structure of data must reflect the hierarchy or levels
      - races run by horses or horses in a training yard
      - puppies in a litter
      - serial measurements on blood samples from cats.

Multilevel data

- Region
  - Farm/Herd
    - → Cow
      - → Lactation
        - → Milk production
- Region
  - → Veterinary practice
    - → Owner
      - › Cat
        - → Body weight
- → Horse
  - → Mask
    - → Exercise
      - → HR, PIF, PEF, etc

For statistical analysis all data should be in codes or numbers

- some statistical programs will not accept categorical variables in the form of letters
- coding should be consistent
- categories must be clearly defined and mutually exclusive
- keep a list of coding

Data entry

- Dates - Use same date format throughout
  - enter as dd/mm/yy in Excel and date will be shown in cell as mm/dd/yy but should be stored as dd/mm/yyyy!
  - Safest option is to format column as dd-month-yy so that if you enter 08/03/04 it shows in the cell as 08-Mar-04

Data management

- Data sets
  - Original data set
    - keep the data set as originally entered and leave it untouched so that you can always go back to see where corrections have been made
  - Verified data set = corrected data set.
    - a copy of the original data set, updated with all corrections
  - Working data sets
    - these are copies of the verified data set

        - containing new variables that are created during the process of carrying out the analysis
    - Naming data sets
        - raw data.xls or TL IVDD raw data.xls
        - TL IVDD 02.xls
        - TL IVDD 03.xls
    - Backup copies!
- Data checking and editing
    - Data checking
        - Print out small data sets
        - Frequencies - maximum and minimum values
        - Cross-tabulations – check for logical relationships & non-sensical values
            - eg male cat that had C-section
            - Spelling inconsistencies – eg breeds
        - Missing values – number of valid observations for each variable
- Keep a data log
    - List of all data files
    - New variables
    - Merged data sets

TL IVDD 01.xls = original file of raw data
TL IVDD 02.xls = breed codes combined,
4 records/cases with a lot of
missing data excluded from further
analysis
TL IVDD 03.xls
etc.

Data analysis

- Statistical analysis
    - Descriptive statistics
        - frequency distributions, ranges
        - histograms, stem and leaf plots, box plots
        - check logical relationships
        - descriptive statistics
        - cross-tabulations
    - Inferential statistics
        - hypothesis testing
        - parameter estimation
        - modelling
- Three steps to go from a conceptual model to a statistical model

1. Consider the type of the outcome variable (response or dependent variable)
   i. categorical or qualitative
      a. binary/dichotomous - nominal or ordinal
      b. > 2 categories - nominal
         ranked - ordinal
   ii. continuous or quantitative - interval - ratio
2. Decide (identify) what your independent units of observation are (a design issue)
   i. individuals
   ii. individual observations made repeatedly on individual animals
   iii. farm, flock, pen, litter, etc.
3. Consider the type (distribution) of independent variables (predictor or explanatory and potential confounding variables):

Types of data (NOIR)

Variable	*Data*	*Description*	*Examples*
Categorical	Nominal	Named categories, no implied order.	Blood groups, breed, sex.
	Ordinal	Ordered categories, where the differences between cancer staging categories are not necessarily equal	Scoring systems,
Numerical	Discrete	Observations can only take certain numerical values	Counts of events, number of offspring
	Continuous - Interval	Equal distances between values but the zero point is arbitrary.	IQ, ordinal data with equal-appearing categories
	- Ratio	And a meaningful zero: data usually measured	Weight, age, temperature, BP

- There are 4 broad classes of statistical methods, depending on the distribution of independent and dependent variables:
  - Statistical models evaluate how much of an outcome occurred (eg with linear regression) or whether an outcome event occurred (eg with logistic regression).
- This approach can be extended to include 'messy' data.
  - Methods to account for correlation among repeated observations and to deal with time-to-event data.
  - Survival analysis – time to failure or event

		Y = dependent variable or outcome	
		Categorical (qualitative)	Continuous (quantitative)
X = independent or predictor variable	Categorical (qualitative)	Contingency tables and chi-square/ Fisher's exact tests	T-tests and ANOVA
	Continuous (quantitative)	Discrete data analysis eg logistic regression	Linear regression and correlation

Clinical observations are susceptible to bias

- Non-participation and loss to follow-up.
- Differential recall of past events and exposures in cases vs. controls.
- Characteristics such as feelings of pain, comfort, and performance are more difficult to measure objectively compared with physical characteristics such as weight, red blood cell count, etc.

The role of bias

- "a process at any stage of inference that tends to produce results that are systematically different from the truth."
- Treatment A was found to work better than Treatment B.
    - But it was also found that the patients in Group A were healthier than the patients in Group B.
    - Or that Treatment A tasted better than Treatment B and was easier to administer so Group A got more of the medication than Group B.

How avoid or minimise sources of bias

- Design
    - Careful consideration of sampling frame and selection of study population.
        - Minimise non-participation.
    - Careful consideration and measurement of potential confounding variables.
    - Consider restriction (exclusion criteria), stratified sampling, matching.
- During the study
    - Careful data collection and measurement of variables.
    - Maximise follow-up.
    - Treat all groups equally.
- Analysis
    - Selection bias cannot be controlled for in analysis.
    - Confounding can be controlled for in the analysis.
        - Stratified analysis
        - Multivariable (regression) analysis to adjust for multiple predictor variables.
        - Matched analysis

A final word on bias

- A potential for bias does not mean that bias is actually present in a particular study.
- To deal effectively with bias, one must
    - Know where and how to look for it

    - Know what can be done about it
    - Determine whether bias is actually present and how large is it likely to be.
- To decide whether bias was important enough to change the conclusions of a study in a clinically meaningful way.

The role of chance

- Observations about disease are made on a sample of patients rather than all those with the disease in question.
    - These observations may misrepresent the situation in the population as a whole because of chance.
- If the observations are repeated on many such patient samples, results for the samples would vary about the true value.

Chance

- The divergence of an observation on a sample from the true population value, due to chance alone, is called random variation.
    - (vs. systematic variation or bias)
- Chance can affect all the steps involved in making or collecting clinical observations.
    - Selection of study subjects
    - Measurement of variables of interest
    - Comparison of groups
- In the assessment of tx.'s A and B, random variation occurs in the sampling of patients for the study, the selection of tx. groups, and the measurements made on the groups.
- Unlike bias (which deflects values in one direction or another), random variation is as likely to results in observations above the true value as below it.
- As a result, the mean of many unbiased observations on samples tends to correspond to the true value in the population, even though the results of an individual sample may not.
- Statistics can be used to estimate the probability of chance (random variation) accounting for clinical results.
    - A knowledge of statistics can also help reduce this probability by allowing one to plan the study design and analysis.

Hypothesis testing

- Hypothesis testing: comparison of groups of subjects.
- Effect = numerical value corresponding to the comparison of interest.
- Statistical null hypothesis = Ho: the effect of interest is 0.
- Alternative hypothesis = H1 or HA: the effect of interest is not 0.

- Evaluate the probability that we could have obtained the observed data (or data that were more extreme) if the null hypothesis were true.
  - This probability is the p-value.
- This is called hypothesis testing because of the aspect of deciding whether or not we can reject the null hypothesis.
- Statistical hypothesis testing calculates the probability of observing our data (or more unlikely data) when the null hypothesis is true.
- Probability of having observed our data (or more extreme data) when the null hypothesis is true.

P-value

- Misinterpretation of P-values:
  - The P-value is not the probability of the data having arisen by chance.
  - It is also not the probability that the observed effect is not a real one.
- It is not possible to evaluate the probability of the observed effect being a real one.
  - The observed effect in the sample is genuine but we do not know what is true in the population.

A clinical trial that looks at whether Drug A is better than Drug B:

		True state of affairs	
		Drug A is *better* than Drug B	Drug A is *no better* than Drug B
Conclusion drawn from a clinical trial	Drug A is *better* than Drug B	Correct (1 -ß = power)	Type I error (risk of making this error = α or the P value)
	Drug A is *no better* than Drug B	Type II error (risk of making this error = ß)	Correct

Results of hypothesis testing

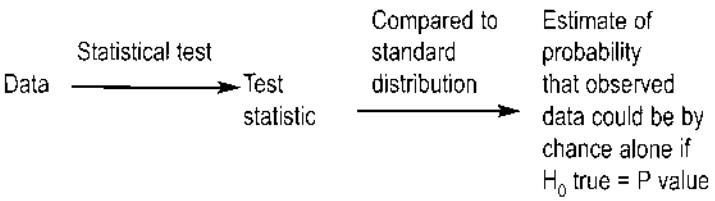
		True difference	
		Present	Absent
Conclusion of a statistical test	Significant difference	Correct (1 - = ß power)	Type I error (α)
	No significant difference	Type II error (ß)	Correct

If $P \geq 0.05$, then the data allow one to reject the null hypothesis and conclude that there was a difference/significant treatment effect/association.

But if $P \leq 0.05$, then the data fail to reject the null hypothesis and one must conclude that there was no significant difference.

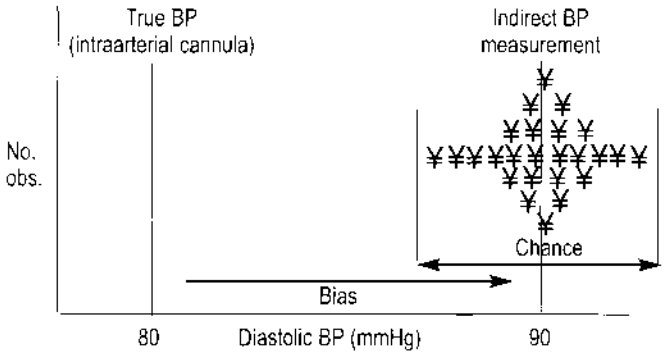
α, ß and power

- The values for α, ß and power are conventionally set at 0.05, 0.2 and 80%.
- But α could be set at 0.01 for 99% confidence or 0.1 for 90% confidence in the results.
- And ß could be set at 0.01 for 99% power or 0.1 for 90% power.



Type III error = answering the wrong question.

Relationship between bias and chance



Measurement of diastolic blood pressure on a single patient. True BP can be obtained with an intra-arterial cannula and is 80 mmHg for this patient. For routine measurements, BP is ordinarily measured indirectly using a sphygmomanometer. This simpler instrument is prone to error or deviations from the true value. This error is represented by all of the sphygmomanometer readings falling to the right of the true value. The deviation of sphygmomanometer readings to the right (bias) may have several explanations – poorly calibrated sphygmomanometer, wrong cuff size, hearing-impaired clinician. Individual BP readings are also subject to error because of random variation in measurement, as shown by the spread of sphygmomanometer readings around the mean value (90 mmHg).

These 2 sources of error, bias and chance, are not mutually exclusive. In most situations, both are present.

Sample size calculations

- How large a sample do I need to conduct this study?

For a study to have a reasonable chance of answering the research question it addresses there must be enough subjects.

Where a study is to look at a single group, the sample should be large enough to give a suitably small standard error for the quantity estimated.

Where 2 groups are to be compared, a power calculation determines how many subjects are needed to have a reasonable (usually 80% or 90%) chance of detecting a clinically important difference between 2 groups.

- Why do sample size calculations?
  - To have a high chance of detecting, as statistically significant, a worthwhile effect if it exists.
  - And, thus, to be reasonably sure that no such benefit exists if it is not found in the study.
- The greater the power of a study, the more sure one can be of the observed results.
  - But greater power requires a larger sample.
- Aim to have a sample size large enough to have a good chance of detecting any clinically important differences and yet not so large as to be wasteful of patients or resources.
  - Inadequate sample size can lead to biologically or clinically meaningful treatment differences that are overlooked and parameter estimates that lack precision.
- Statistical techniques exist for determining the optimal sample size in different circumstances for both experimental and observational studies.
  - However, these calculations usually depend on our having some idea of the results we expect at the end of the study.
- Clinical trial to investigate the effect of a new drug or surgical procedure.
  - Is the new treatment better than existing treatments or no treatment (placebo)?
  - Estimate of effect

- $\alpha = 0.05$
- $\beta = 0.20$
- Clinically significant difference
- Rate of events in patients on conventional tx.
- Number of patients in each tx. group

- If you know 4 out of these 5 elements, you can calculate the 5th.

Suppose we want to know how large a sample would be needed to compare the means of a continuous variable using 2 independent groups. The comparison can be done using a two-sample T-test as long as the outcome is normally distributed and the groups have approximately equal variances. We need to specify four elements to use Altman's nomogram.

Two independent groups, continuous data

- To calculate the sample size = Number of patients required in each group.
- $\alpha = 0.05$
- $\beta = 0.20$ to give 80% power
- Clinically significant difference as the treatment effect = δ
  - Difference in means that is important to you and which you do not want to overlook
- Standard deviation of observations in each group = σ = SD
- Assuming constant variance
- Standardised difference = d = δ/SD

Example

- Planning a trial to look at comparing mean body weights at the time of mating in 2 groups of female Vancouver Island marmots:
  - One group was flushed (fed on a high plane of nutrition) and one group was not.
  - Average weight of female marmots caught in the wild in May is 3 kg 0.22 (SD)
- Treatment effect = δ
  - 0.25 kg increase in body weight on a high plane of nutrition.
- Standardised difference = d = /SD
- = 0.25/0.22 = 1.14
- Altman's nomogram: 24 total or 12 per group
- Winepiscope: 15 per group
- But there are <100 left in the wild and only about 30 in captivity, with a little more than half of these being females ...
- ... so, if we hope that our diet is really good and the treatment group gains 0.5 kg, then
- Winepiscope: 6 per group
- Calculate the power of study if only 16 animals total (8/grp) sampled with = 0.25 (tx. effect) and d = 1.14.

Suppose we want to know how large a sample would be needed to compare 2 proportions in 2 independent groups using a Chi-squared test. For example, the groups could be patients having a disease vs. being healthy or being dead vs. alive.

So if we know the proportion, p1, that we expect in one group, then we make the proportion, p2, in the other group a value which makes the difference in the 2 proportions, p1 – p2, represent a relevant difference.

Two independent groups, categorical data

- To calculate the sample size = Number of patients required in each group.
- $\alpha = 0.05$
- ß = 0.20 to give 80% power
- Clinically significant difference in the 2 proportions, $p_1 - p_2$.
  - So if we know p_1 as what we expect in one group, then we make p_2 take a value that makes the difference in the 2 proportions, $p_1 - p_2$, represent a relevant difference.
- Standardised difference = d = $p_1 - p_2$/sq rt (p(1-p)
  - where p = $p_1 - p_2/2$

Example

Circumcostal Gastropexy (CCGP) vs. Gastrocolopexy (GCP)

- p_1 is the proportion of dogs undergoing CCGP that suffer recurrence of GDV = 9%
- p_2 is the proportion of dogs undergoing GCP that suffer recurrence of GDV = 20% a
- the difference in the 2 proportions, $p_1 - p_2$ = 11% represents a clinically important difference.
- Standardised difference = d = $p_1 - p_2$ /sq rt(p(1-p)
  - where p = $p_1 - p_2$ /2 = 0.31
- Altman's nomogram: ~ 325 dogs or 163 per group.
- Winepiscope: 158 dogs per group.

	Recurrence of GDV		
Procedure	Yes	No	
CCGP	2	20	2/22 = 9% = p_1
GCP	4	16	4/20 = 20% = p_2

As I said, there are statistical techniques for determining the sample size needed in different circumstances for both clinical trials and observational studies. The problem is that these calculations require some idea of the results expected at the end of the study before it has even been conducted!

To paraphrase Norman and Streiner

Sample size calculations are based on a hope and a prayer because they require such heroic assumptions about the likely differences you will encounter at the end of the study.

In fact, the only time really defensible sample size calculations can be done are after the study is over because only then will you have decent estimates of the required parameters.

The real talent is the ability to fiddle all those numbers through several iterations so that the calculated sample size precisely equals the number of patients you wanted to use in the first place (or how many you can afford to enroll in the study)!

A final word

- Planning, planning, planning.
- Keep it simple and do not assume that a statistician will be able to show you how to analyse your data.

"Photonumerophobia: the fear that one's fear of numbers will come to light".

Norman and Streiner 1994

Acknowledgements

Dr Hugh Townsend, University of Saskatchewan

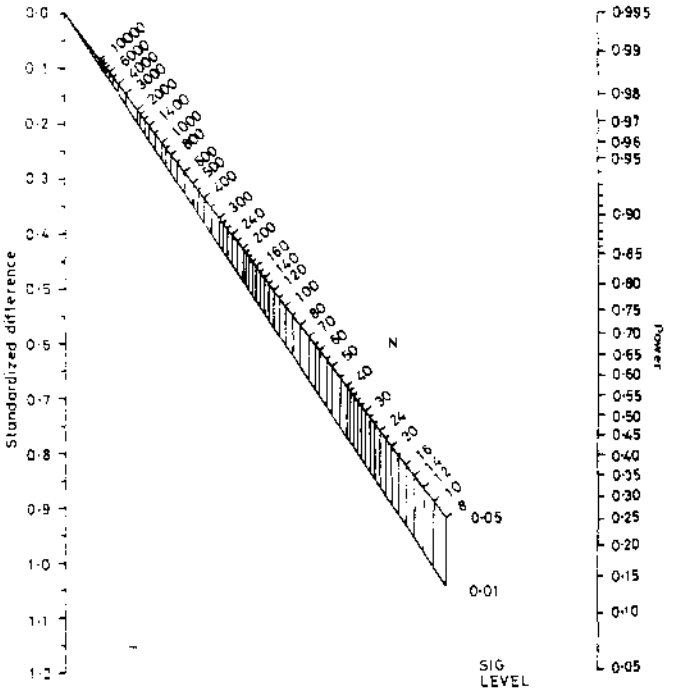


Figure 15.2 Nomogram for calculating sample size or power (reproduced from Altman, 1982b, with permission)

R. Eddie Clutton
Easter Bush Veterinary Centre, Easter Bush, Roslin, Midlothian EH25 9RG, UK

The ECVA requires that

> *As from the year 2001 the deadline for submitting an application to sit the exams is* ***1st March*** *in the year the exam is taken. Everything must be submitted by this date with the exception of the original paper. The latter, or a letter from the editor of an internationally refereed scientific journal certifying the FINAL acceptance of the paper, may be received by the Secretary no later than 1st July of the same year. If the original paper is in a language other than English, the candidate should provide an extensive summary in English. The original paper as well as the 3 case reports should be related to anaesthesia/intensive care.*
>
> ***If any submitted work is considered to be of inadequate quality, the candidate will not be allowed to proceed further with the examinations.***

The mature resident with a PhD or MSc (or similar degree) with pre-existing publications, work submitted or 'in press' is in an enviable position, but should check with their supervisor as soon as beginning the residency that the work is suitably relevant to anaesthesia and intensive care. If any doubt exists the Chairman of the ECVA examinations committee must be consulted.

The first 6–9 months

The single biggest problem with the Diploma project is the steady passage of time, which proceeds at a rate of 24 h per day. The first step to planning the project is deciding in which year the examination is to be taken. Of the 6 components of the project

1) Establish enquiry
2) Literature review
3) Preparation: ethical approval/feasibility/pilot study/power calculation/consultation/consent/HO licensing
4) Data collection
5) Data analysis
6) Writing up
7) Submission/review/acceptance/rejection

the last component is the least controllable. Previously *Veterinary Anaesthesia* and Analgesia had a sympathetic 'acceptance' policy to ECVA examination delegates which meant that no applicant failed to meet the submitted publication criteria for exam entrance. Other journals may be less sympathetic. Consequently, if other journals are considered, their submission to acceptance period should be calculated, bearing in mind that both author and reviewer responsiveness influences this.

1) Establish enquiry

Intellects may pursue their own line of investigation. Please make it nteresting. The best ideas aim to solve real problems in veterinary species; not mimic. Research on new drugs, new species, new equipment or mimicking medical research is valid if conducted properly. Recent graduates may require inspiration (or orders) from their supervisor or more experienced colleagues. It is worth checking what other lines of research are going on locally that would accommodate 'piggybacking' or collaboration. In the latter cases, residents must take a 'central' role otherwise the viva examination may disclose the truth!

2) Literature review

Once an idea is established a literature review is conducted. This can be done electronically to begin with, but a visit to the library is inevitable for a full review, particularly with relatively 'brief' search engines.

3) Preparation

If the search reveals an unexplored or *poorly researched* line of enquiry, then several things need to be done at the same time.

a) Study design; consult colleagues/supervisor/statistician to discuss the way in which the question can be best answered. Methods of randomisation and the need for control groups need to be considered

b) Determine if the proposed study is ethical? See colleagues/ supervisor and eventually submit a proposal (which forms the basis of the introduction) the ethical review process. Consider client consent forms (in conjunction with hospital director/primary clinicians) or Home Office licensing

c) Most important. Establish whether the research objective can be achieved in the resident's working environment, ie are there enough cases presented/animals available per unit time to realistically get enough data. how many people are required to collect data? Is the hardware required available? Are 'primary' clinicians going to be co-operative? How feasible is it to control the most important variables. How stressed are add-ons going to be. Is the resident expected to manage several cases simultaneously? Might the study be best achieved during 'study time'. Might

students or nurses be able to collect the data. Will out-of-hours work be required, ie pain behaviours? Does the methodology fit in with long lists.

(When there is an inordinately small case load, consider anatomic (cadaver studies), something observational in the local PDSA, a retrospective study of existing case records)

d) Pilot study. Once everyone is satisfied with the study design and methodology, a pilot study is conducted to determine if the expectations are realistic. An ideal study would be one in which the resident could collect quality data without relying on anyone else, or without the data collection being disrupted by competition for equipment etc. Can the data be easily and accurately collected by colleagues? This maximises the amount of animals that can be studied. 'Fine tune' the type and frequency of data analysis.

e) Preliminary data collected in the pilot should be submitted for power analysis.

f) Confirm methodology, produce notated version for participating colleagues

4) Data collection

If this cannot be performed electronically a paper data collection sheet must be designed in conjunction with a laboratory book/diary. A spread sheet should also be established for recording accumulating data. This should be easily completed and formatted in a way that suits the Stats package that is to be used. Full notes should be taken during the study for possible use in the review process. During 'free' periods the resident should collect 'Footnote' information.

5) Data analysis

See your statistician.

6) Writing up

The paper should be near complete by this stage. The introduction should have been completed by the 'proposal' stage, while the materials and methods can be done once the methodology is demonstrably sound and repeatable. The results and discussion will depend on the statistician.

7) Submission

Before submitting, supervisors and all co-workers must have reviewed and approved the paper. The cover letter (or e-mail) should include a statement that the work is intended to meet examination eligibility criteria and diplomatic plea for rapid processing to the stage of acceptance. Editors will, however, ignore pleas for 'fast-tracking' if the resident 'dawdles' over revision and re-submission.

K. Dunn
21 High Street, Barton, Cambridgeshire CB3 7BG, UK

The key to success in publishing in research is to meet the needs of the reader. There is an increasing array of veterinary publications but they are all striving to satisfy their readership (which is the limited pool of veterinary surgeons).

1. What do journals want

Publications basically fall into 2 categories those for which:

1. ***subscriber numbers*** are important
   – these publications are often heavily reliant on advertising revenue and there is nothing advertisers like better than a large (captive) audience.
2. ***impact factor*** is important
   – these publications are looking for particularly 'valuable' papers which will be judged by
   i) Novelty of report
   ii) Research areas where rapid advances are being made
   iii) Quality of research

Publications in the first category will be looking for material that interests their readership, and preferably that relates to a hotly advertised topic. Those in the second category will look primarily at the quality of the research and will be considering how any given submission will affect their impact factor.

1a) What is an impact factor?

The impact factor of a journal is a measure of the frequency with which the 'average article' in a journal has been cited in a particular year or period. It is usually calculated by dividing the number of current year citations to the source items published in that journal during the previous 2 years.

If 100 articles have been published in a given journal in the last 2 years and in that period there have been 100 citations to articles in the journal IF = 1. Impact factor is a better measure of a journal than absolute citation numbers as this removes some of the bias which would otherwise favour larger journals or older journals (with a larger body of published material).

The impact factor of a journal is particularly important to authors from academic institutions because they are judged on a research assessment exercise which grades published research according to the IF of journals.

1b) What is high quality research?

Strictly speaking high quality research is that which is carried out with scientific rigour and the conclusions draw are valid. In some areas (notably social sciences) qualitative research is important and highly regarded in veterinary medicine quantitative research is often rated more highly. Studies are often ranked according to the study method, but in truth different types of study are valid under different circumstances. The following study types are seen most often in medical literature:

Short communication

Should be used if a case has a single novel aspect from which the profession would benefit by rapid dissemination of the information.

Case reports

Case reports should describe the first report of a novel condition or therapy (or at least the first report in a certain geographic location where location is relevant). If the report is not novel it would only be considered for publication if it materially adds to the literature and in all cases a case series would be preferred. Case reports may review any previously reported single case reports and draw together similar information as provided in a case series in this way.

Case series

Will always be preferred over case reports. A case series usually includes between 2 and 7 similar cases. By reporting a number of cases together more conclusions can be drawn

Cohort studies

One group of patients is exposed to a factor or treatment and compared to another group that has not been exposed.

Randomised control trials

The least common form of study in veterinary medicine but the most powerful study design if correctly performed. Involves at least 2 groups (at least one treatment and a control) to which patients are randomly assigned. Ideally no-one knows which treatment group patient is in. However, these studies are expensive and it may be unethical to withhold treatment for a control group.

Retrospective study

A retrospective study involves examination of existing data. These studies are advantageous in that they can easily include a relatively large number of cases and since all data already exists results can be produced quite quickly. However, their usefulness relies on the quality of the original data collection, which, in veterinary medicine, is often found wanting.

Prospective studies

Increasingly being performed in veterinary practice and if designed appropriately can produce high quality data. The essential advantage over prospective over retrospective studies is that accurate and full data collection can be ensured.

Review papers

A good review can be very useful – it should be a comprehensive survey of all available evidence in a particular area. Systematic reviews provide unbiased summaries of the available evidence and are more than a descriptive 'listing' of the findings of various scientific studies. This paper should be a thoughtful integration of the results and ideas from previous studies and provide a new perspective or understanding or provoke discussion within that field. The conclusions of a previous studies need to be placed in relation to one another... do they agree? (and if not what factors of the studies might explain the discrepancy).

2. Choosing the right journal

In order to satisfy your own needs and that of the journal you must make a careful selection of where to submit your work.

First, consider why you want to publish:

For the 'greater good' (knowledge dissemination)
Peer recognition
To become generally well known in your field
Impact factor rating or CV fodder
Needing publication as qualification for an examination!

Think about the audience you are trying to reach as this will affect your choice of journal:

- Do you need your name to be known in academic circles?
- Or are you trying to educate/ inform GP vets (or to encourage them to refer cases to you)?

Select a journal known to be read by this group.

You may be looking for rapid turn around of paper (short time to acceptance or publication):

- If you need to get a paper published for a particular deadline (examination entry!) you may just need a letter of acceptance
- If you feel the work is of such value that it must be rapidly communicated you may choose a journal that publishes online ahead of print.

The impact factor may be important but the IF of most veterinary journals ranges from 1-X. These are all relatively humble figures when compared with the scores of XXXs that can be achieved by the top science journals.

3. Preparing the paper

Before you sit down to write:

1. Think again about the study you have done and your conclusions - are they genuinely novel, of high quality and will your paper be of interest to readers?

2. Read some issues of the journal to which you expect to submit your paper and take note of the style and content (confirm that your paper will sit well with the existing material).

3. Read the instructions to authors (and abide by them!)

   a. Word limit

   b. Format of refs

   c. Layout eg line numbering double spacing etc (all these rules are made for a reason).

4. Start writing.

Writing tips

It is always hard to start writing so begin wherever you feel most comfortable (the methods section may be the most straightforward) and get a first draft onto paper without worrying too much about it. It is much easier to make amendments when you have something to work with!

Once you have a rough draft, start to order your thoughts and construct a logical sequence to the paper. Before making any editorial changes review the 'Author Guidelines' of the journal to which you plan to submit. It may help to use as a guide a similar paper already published in your chosen journal.

Carefully review your paper and revise the text to express your thoughts in the fewest words possible. Avoid using the same nouns or verbs in close proximity. However, you can repeat key points if you think it would be meaningful. Editors (and readers) appreciate brevity and you must keep within the word limit – if you genuinely have too much to say for this to be possible then you probably have enough material for 2 papers! Continue to revise your ideas until they are expressed as succinctly as possible.

Although it may seem unfair, a paper will inevitably be judged partly on its style and readability. It is more likely to be accepted if it is not only sound scientifically but well written and concise. Reviewers are more apt to reject a manuscript that does not read well and is not well organised. Sloppy writing, typographical mistakes and errors in tables suggest careless work. The reviewers must be able to understand the work and your conclusions on a first read through the paper. If they (as experts in this field) are unclear about what you are trying to say, how can you expect the average reader to understand your work.

It should always be clear which ideas are yours and which ideas (and words) are cited from other papers. Try not to cite something that someone else has cited ('chain citation'). Always go back to the original paper. even if this means getting important foreign papers translated. Remember the rule – if you are going to cite it you must have read it.

Once the first draft of the paper is prepared:

1. Have coauthors read, contribute and review paper and make modifications as necessary.
2. Ask a colleague not involved with work to read paper and listen to their criticisms.
3. Acknowledge and assistance/ funding.
4. Proof read paper (check spellings US vs UK) and CHECK REFERENCES it is all too easy to remove or insert references as you are revising paper and to forget to put them in the reference list. Make sure abbreviations are all explained the first time they are used.
5. If you are a non-native speaker of the language of the paper then ask someone else to read and correct it. It is unfair to make the reviewers struggle with a poorly written paper as well as try to make constructive remarks on the science.

4. What happens to paper when submitted?

Journals differ in how papers are handled on submission. In most cases the paper would be assessed by the editor or editorial board to establish that it is something that the journal might be interested in. Some papers will be returned at this stage because they don't meet the inclusion criteria for the journal - if you have prepared properly this should not happen.

Scientific papers are usually submitted to peer-reviewed journals. The peer-review process is a useful quality control exercise for scientific paper publishing. A number of peer-reviewers (professionals active in the field of the work but ideally from a different institution to the authors) will be selected. Some journals allow authors to suggest reviewers for their paper and this can be helpful, particularly when the paper is in a field on the edge of the normal content of the journal where reviewers may be scarce.

Copies of the paper will be sent simultaneously to the selected peer-reviewers who are asked for comments within a specified timeframe (usually 3-4 weeks). Peer- review (when done properly) is onerous and time-consuming but is generally accepted as the best way to provide quality control on scientific publications. In the majority of cases reviewers undertake the task for the 'greater good' as most journals do not pay reviewers at all and those that do come nowhere near a realistic payment for time spent.

Comments from the reviewers are returned to the editor who will review the paper and the comments to make a decision on the paper. It may be necessary to take further advice at this stage or comments may be communicated to author.

In most journals the reviewers remain anonymous (although some medical journals operate an open reviewing system where authors are aware of who has commented on their paper).

5. Dealing with comments

The response from the journal will usually fall into one of 5 categories

1. Accept – this is extremely rare on the first submission of a paper - in most cases there will be comments to be addressed.

2. Accept with amendments – if the amendments are minor the editor may simply request that the author makes the changes indicated and that the paper then goes straight through to publication.

3. Amendments required – the usual outcome for most papers. The reviewers are saying that essentially the paper appears sound but they have identified some areas that require reworking and would like to see the paper again before it goes to publication.

4. Rewrite and resubmit – do not be too disillusioned by this response. It means the journal is interested in what you have to say but considers there are some serious flaws in the paper or its preparation. Look carefully at what the reviewers have to say and you may be able to reformat the paper accordingly or provide additional results to back up your claim.

5. Reject – most papers are rejected because they do not meet the needs of the journal. This probably means that you have submitted your article to the wrong place. Remember that most journals receive many more submissions each year than they publish papers so they would have to reject a significant number of papers even if all the papers were of good quality.

Consider the reviewing process as an aid to production of a high quality paper. Do not take reviewer's comments personally. A good reviewer should provide constructive criticism. Once the paper has been revised to address the questions raised by reviewers it should be better for the changes.

However, if you do have a valid argument against a reviewer's suggested changes include some additional comment in the paper (do not just put this argument to the reviewer). If the reviewer has misunderstood or misinterpreted what you were trying to say then others will do so too.

Always make a polite and detailed response to corrections. Changes to the text should be highlighted in the altered draft and ideally a separate list prepared indicating where changes were made (by line number).

It is in your own interest to respond rapidly to corrections and resubmit as

soon as you can because:

- The information will still be fresh in everyone's mind which means that the reviewer does not have to start from scratch when examining the changes to the paper.
- You reduce the risk of others getting to publication first with the same work
- There is more chance that the same reviewer will check the corrections. If the first reviewer is unavailable when the paper is resubmitted it is inevitable that a fresh pair of eyes will draw out a whole new set of corrections. This is extremely frustrating for editor and author.

This meeting is dedicated to the memory of Dr Roman Skarda