Pharmacoepidemiology and pharmacoeconomics - Principles and practice

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Overview

• Brief outline of the methods of pharmacoepidemiology
• More detailed introduction to the methods and applications of health economics
Pharmacoepidemiology

• Defined as the study of the utilization and effects of drugs in large numbers of people
• Application of epidemiology to clinical pharmacology
Pharmacoepidemiology in practice

- To quantify adverse events with medicines in the population
- Identify rare events
- Patterns of drug utilisation, including adherence
- Hypothesis generating
Research Designs

• Analytic Studies
  – Experimental Study - RCT
  – Prospective Cohort Study
  – Retrospective Cohort Study
  – Case-Control Study

• Descriptive Studies
  – Case Series
  – Case Reports
Timeframe of Studies

• Prospective Study - examines future events, follows patients into the future
Timeframe of Studies

• Retrospective Study - looks back in time to study events that have already occurred
Prospective Cohort study

Measure exposure and confounder variables

Baseline

Exposed → Outcome
Non-exposed → Outcome

Study begins here
Retrospective Cohort study

Measure exposure and confounder variables

Baseline

Exposed → Outcome

Non-exposed → Outcome

Study begins here
Case-Control Design

Study

population

Drug present

Drug absent

Drug present

Drug absent

Cases

(ADR)

Controls

(no ADR)

Study begins here

past

present

time

Study begins here
Biases in observational studies

• Confounding by indication
  – Patients who need treatment are more likely to receive treatment

• Unmeasured confounding
  – Association between ice cream sales and shark attacks

• Choice of exposure risk-windows
  – Sufficiently long to capture the event (e.g. ADR)

• Time-related biases
  – E.g. difference over time in reporting /recording certain outcomes
Health Economics

• Demand for healthcare is infinite
  – increased expectations and technological change

• Resources are scarce
  – money, doctors, hospitals

• Choices are necessary
  – should we use a new monoclonal antibody?

• Prioritisation is required
  – on what basis?

• Costs and benefits must be compared
  – how do we measure benefits?
Opportunity cost & cost-effectiveness

• By choosing to use resources in one particular way, other opportunities for using these resources are forgone
• National Institute for Health and Care Excellence (NICE) requires favourable and convincing evidence on cost-effectiveness before approving new health technologies
• Aim to maximise population health given finite resources
Healthcare resource use & costs

• Cost perspective is normally that of the NHS and personal social services
  – However, wider societal benefits, considering out-of-pocket expenses, indirect costs such as days off work etc. might feature increasingly in NICE appraisals

• Generally limit data collection to disease-related services
Healthcare resource utilisation

- Measure directly from trials or observational studies
- Sometimes experts are asked
  - Opinions do not rank highly in the hierarchy of evidence
- Increase reliance on data collected routinely
  - E.g. Hospital Episode Statistics (HES)
.. and cost

- Unit costs are derived from standard sources
  - BNF, NHS reference costs etc.
- Total cost is the sum-product of items of resource use and unit costs
- Total cost = $\Sigma_i \ (\text{resource}_{ij} \times \text{unit cost}_j)$
Costs - properties

• Non-normally distributed
• Non-negative and positive skewed
• Decision-makers interested in mean cost
  – Arithmetic mean x total number of patients = total cost
Costs
Discounting

• Time preference: costs and benefits have greater value in the PRESENT

• $PV = \sum Fn (1 + r)^{-n}$
  – $PV$ = present value
  – $Fn$ = future cost at year $n$
  – $r$ = discount rate

• Recommended discount rate for both costs and benefits is 3.5% per annum
Example

\[
\frac{5}{(1+0.035)^1} + \frac{10}{(1+0.035)^2} + \frac{15}{(1+0.035)^3}
\]

<table>
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<tr>
<th>Year</th>
<th>Cost of Prog A (£000s)</th>
<th>Cost of Prog B (£000s)</th>
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<tr>
<td>TOTAL PV</td>
<td>26.79</td>
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</table>
Types of economic evaluations

- Cost minimisation analysis
- Cost effectiveness analysis
- Cost utility analysis
- Cost benefit analysis
- Cost consequence analysis
QALYs

• Composite of health-related quality of life (expressed in utilities), and the time spent in each state of health

• Utilities are confined to the interval:
  – 0 (death) to 1 (full health)

• However there are states worse than death:
  – Confined to bed, Unable to wash/dress, Unable to perform usual activities, Extreme pain/discomfort, Extremely anxious/depressed
  – EQ-5D rating of -0.594
Utility weights

• Registration trials do not routinely include measures of utility
• NICE submissions sometimes include a ‘mapping’ of clinical QoL data onto utility scales
  – Not always reliable
Utility weights

• Preferred instrument is EQ-5D-3L (or 5L)
  – or alternative e.g. standard gamble, time-trade off, EQ-VAS measured directly in from patients
• EQ-5D generates a preference score that represents the general public’s preference for the health state
• The alternatives measure patient preferences
Your own health state today

By placing a tick in one box in each group below, please indicate which statement best describes your own health state today. Do not tick more than one box in each group.

**Mobility**
- I have no problems in walking about
- I have some problems in walking about
- I am confined to bed

**Self-care**
- I have no problems with self-care
- I have some problems washing and dressing myself
- I am unable to wash and dress myself

**Usual activities (e.g., work, study, housework, family or leisure activities)**
- I have no problems with performing my usual activities
- I have some problems with performing my usual activities
- I am unable to perform my usual activities

**Pain/discomfort**
- I have no pain or discomfort
- I have moderate pain or discomfort
- I have extreme pain or discomfort

**Anxiety/depression**
- I am not anxious or depressed
- I am moderately anxious or depressed
- I am extremely anxious or depressed

Your own health state today

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is.
Clinical inputs

• Efficacy or effectiveness?
  – May have been derived from more than one trial
  – Appropriate systematic review and meta-analytic techniques required
  – Beware of selective use of sub-groups
  – ..and inappropriate trials
  – ..and whether the trial evidence ties in with the licensed indication(s)
  – Always interested in the expected outcome e.g. mean survival (= area under the survival curve)
Clinical inputs

• Adverse events
  – Important source of morbidity and costs in many instances
  – Need to make sure that the incidence of ADRs used in the model reflects that observed in the trial (or other) data source
  – And that HR-QoL adjustments are made
Plausible QALY gains
25% of 30 months
= 7.5 months
= 0.63 years
B  Progression-free Survival

Progression-free Survival (%) vs. Months
B  Progression-free Survival

Progression-free Survival (%) vs. Months
11% of 7 months + 9% of 48 months
= 0.8 + 4.3 months
= 0.42 years
Plausible QALY gains

• 0.63 yrs (of life) x 0.6 = 0.38
• 0.42 yrs (of PFS) x 0.2 = 0.08

• QALY gain = 0.46
ICERs

• Incremental cost effectiveness ratio

\[
\text{ICER} = \frac{\text{Difference in costs}}{\text{Difference in benefits}}
\]

• How much more an intervention costs for an addition unit of benefit
Cost-effectiveness “threshold”

A = £20,000 per QALY gained

B = >£30,000 per QALY gained

Probability of rejection on grounds of cost infectiveness

Increasing cost/QALY (log scale)

Rawlins and Culyer, BMJ 2004;329:224-227
At the margin

• Approving an intervention at £20-30k per QALY is equivalent to direct substitution of QALY gain with a QALY loss
  – no net population health gain

• Approving an intervention of £40-60k / QALY effectively means
  – net population loss of one QALY
Results

• Base-case analysis
  – This is the best guess of the cost-effectiveness

• Sensitivity analyses
  – These try to capture sources of uncertainty in the analysis
Uncertainty

• Sources of data
  – Trial A or Trial B?
  – EQ-5D or SF-6D utility scores?

• Parameter uncertainty
  – Mean +/- SD

• Structural uncertainty
  – Assumptions on long-term treatment effect
One-way sensitivity analysis

• One parameter estimate varied within ‘reasonable’ limits
  – E.g. RR may be varied from lower to upper 95% CI limit

• Multi-way sensitivity is where more than one variable is changed at a time
Probabilistic sensitivity analysis

- Assign distributions to parameters in order to characterise the uncertainty
- Draw 1,000 hypothetical patients from probability distributions (Monte Carlo simulations)
- Plot the incremental cost versus incremental benefit on a cost-effectiveness plane
Distributions

Beta distribution

Log - normal distribution

Probabilities

Costs
Cost-effectiveness plane
Cost Effectiveness Acceptability Curve
Subgroup analyses

• Clinical and cost effectiveness may differ because of differing characteristics of patient populations

• There should be a clear clinical justification and, where appropriate, biological plausibility for the definition of the patient subgroup and the expectation of a differential effect
Model structure – Markov model

- PFS
- Progression
- Death
What is a Markov model?

- Models finite number of defined health states
- Useful for chronic diseases
- Individuals entering model progress from one state to another according to a set of transition probabilities
- Can model progress of a disease over a lifetime
Markov Model Structure

Pt_n = transitional probability
Markov Model Example

- 100 identical patients simultaneously enter the process
- If $P_{t_1} = 0.1; P_{t_2} = 0.3; P_{t_3} = 0.1$
  - At $t=t+1$
    - 80 patients will re-enter PFS
    - 10 will progress to state of disease progression
    - 10 will be dead
  - At $t=t+2$
    - 64 patients will remain in PFS state
    - 15 will be in the state of disease progression
    - 21 will be dead and so on..
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Calculating costs and QALYs from Markov models

- Attach costs and utilities to each health state
- Sum over time
- Gives total QALYs and costs per cohort of (e.g. 100 patients)
- Repeat for treatment A and comparator B
- Calculate ICER
Things to look out for in economic evaluations

• Time horizon of analysis
  – Adequate?
• Choice of comparator
  – Appropriate?
• Uncertainty
  – Addressed?
• Sub-group analysis
  – Valid?
• Measures of health outcome
  – Robust?
KEEP CALM AND ANY QUESTIONS