Within-trial cost-effectiveness analysis with censored data

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METHODS

If patients enter a clinical trial at different times, but the trial analysis takes place on a fixed time point, then longitudinal data will be censored. These data can be assumed to be missing completely at random.

A within-trial cost effectiveness analysis needs to take account of this, to calculate mean differences in cost and effects between treatment groups, and measures of uncertainty, over the length of the trial time period

AIMS

We compare 3 methods for the analysis of censored cost and quality-adjusted life years (QALY) data

1. Use complete cases only, using OLS to calculate mean differences and 95% confidence intervals (Figure 3)

2. Inverse probability weighting (Willan, Lin and Manca 2005), assuming bivariate normality

3. Inverse probability weighting, using joint non-parametric bootstrap to calculate 95% confidence intervals
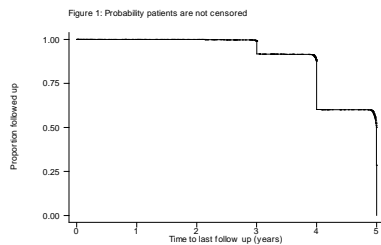

Figure 1: Probability patients are not censored

INVERSE PROBABILITY WEIGHTING (IPW)

Divide the time period of interest into intervals between data collection visits

Estimate the probability G(t) that each patient is not censored up to time t

G(t) can be estimated using a Kaplan Meier survival function, where an "event" is 1 if the patient is censored and 0 if the patient died (reversing the usual definition of an event). See Figure 1

Weight each patients cost (and QALY) during the interval by 1/G(t) if the patient died or survived to at least the end of the interval and 0 otherwise

Calculate the mean weighted difference in cost (and QALY) for each interval (Figure 2) This can be estimated by weighted OLS regression, controlling for baseline characteristics as appropriate

Mean cost over the whole period of interest (and QALY) is the sum of the mean weighted costs (QALY) for each interval (Table 1)

Variances and covariance for mean costs and QALYs can be estimated assuming bivariate normality to calculate confidence intervals for differences in means (Figure 3) and net benefits

Alternatively, these measures of uncertainty can be calculated by bootstrap methods (Figure 3)
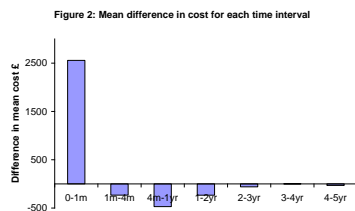

Figure 2: Mean difference in cost for each time interval

APPLICATION

Randomised Intervention Treatment of unstable Angina (RITA-3) (K A A Fox et al 2005)

Patients: unstable angina or non-ST-elevation myocardial infarction

Interventions: early angiography with revascularisation if clinically indicated *versus* a conservative strategy. Both groups received optimum medical treatment.

Follow up: At discharge from index admission, 4 months, 1 year and yearly thereafter up to 5 years post randomisation. Median follow up was 5 years, inter-quartile range was 4.6 to 5 years

COMPARISON OF RESULTS USING DIFFERENT METHODS

Table1: Mean difference in costs and QALYs between treatment groups over 5 years calculated using IPW and complete cases

	Mean difference in cost £	Mean difference in QALYs	ICER £/QALY
Complete cases	1,477	-0.003	Early intervention is dominated
IPW method	1,557	0.080	19,000

Figure 3: Mean difference in (A) costs and (B) QALYs between treatment groups over 5 years calculated using: i) complete cases, ii) using IPW and assuming bivariate normality and iii) using IPW with bootstrap methods

Panel A

Panel B
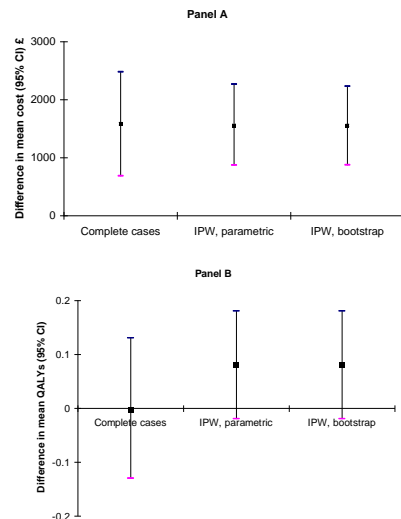
CONCLUSIONS

Complete case analysis is simple to calculate but does not use all the data and can give misleading results

IPW uses all the data and gives unbiased estimates, controlling for baseline characteristics and censoring

IPW with bootstrap gives similar estimates of confidence intervals compared with assuming bivariate normality in this dataset and is easy to calculate

REFERENCES

Andrew R Willan, D Y Lin and Andrea Manca. Regression methods for cost-effectiveness analysis with censored data. Statistics in Medicine 2005; 24: 131-145

K A A Fox, P A Poole-Wilson, T C Clayton et al. 5-year outcome of an interventional strategy in non-ST-elevation acute myocardial infarction. The Lancet 2005; 366:914-920