Using Multicentre RCT-based IPD to Populate Decision Analytic CE Models for Location-Specific Decision Making: a Bayesian Approach

Pedro Saramago

MSc in Health Economics

supervision: Dr. Andrea Manca

THE UNIVERSITY of York

CHE
Centre For Health Economics

APES CONFERENCE

– Porto, October 2009 -

Overview

Section 1 : Background

- Cost-Effectiveness Analysis
- Trials vs Models
- Multicentre/multinational RCTs
- Motivation

Section 2 : Methods

- Multilevel modelling
- Bayesian approach

Section 3 : Motivating example: RITA 3 trial

- Background
- Multilevel analysis results (only a few)

Section 4 : Discussion/Conclusion

Background

- **RCTs:** Estimation of costs and effects directly, e.g. inference using RCT data where costs and effects were collected
- **Incorporate external evidence? Appropriate time horizon given new technology? -> DAMs**: combines information from various sources using mathematical relationships
- **DAMs:** evaluation of expected outcomes with cohort or aggregated models, e.g. decision trees and discrete time Markov chains

Background

- **False dichotomy: Trials vs Models**

  - Models and trials are complements, not substitutes

- **RCT IPD used to populate DAMs:** EUROPA, GOAL and RITA trials

- **Multinational/multicentre RCTs**

  - exchangeability/generalisability of results? correct quantification of uncertainty?

  - datasets with hierarchical structure with potential correlation in costs and outcomes

  - **Hierarchical Modelling** - ideal pathway to analyze CE IPD from multiple location trials allowing for between-location variability

Background

- Relationship between the inputs is too complex to return a 'closed form' solution describing the exact distribution of the estimator for the CE measure -> **Monte Carlo sims**

- **PSA:** reflect the uncertainty in the input parameters and illustrate its consequences on the outputs of interest. Monte Carlo methods can be used to propagate uncertainty in the model over the expected outcome measure

- **2 stage approach:**

  - **1st:** decision model parameters obtained from primary, secondary or elicited data analysis

  - **2nd:** decision model is developed in the form of a spreadsheet in which these parameter estimates are assigned distributions, model evaluated using MC sims

Motivation

- **Develop/apply/explore methodology for the analysis IPD of multicentre/multinational RCTs with the aim of**

  (a) estimating location-specific parameters to populate decision models;

  (b) conducting a Bayesian PSA to evaluate the decision problem

Methods

- **Multilevel / Hierarchical modelling**

  i. account for individual- and location-level variation in estimating location-level regression coefficients

  ii. models variation among individual-level regression coefficients

  iii. estimates regression coefficients for particular locations

  -> Multilevel linear models

  -> Multilevel generalized linear models

  -> Multilevel survival models

  -> Multilevel linear mixed models in a longitudinal data framework

Methods

- **Bayesian approach**

  - alternative to the classical approach of statistical inference

  - removes the need to make parametric distributional assumptions (given the posterior distributions available)

  - MCMC estimation -> Gibbs sampling (WinBUGS)

  - allows prior beliefs to be incorporated, e.g. expert beliefs of clinicians on the likely treatment effect

  - informative or vague a priori beliefs may be incorporated

  Bayes' Theorem

$$p(\theta|y) \propto p(\theta) \cdot p(y|\theta)$$

  - **application of Bayesian inference to DAMs in this context is denominated "one-stage" approach**

Motivating Example: The RITA 3 Trial

- **Multicentre trial conducted in one country**
- **Early intervention strategy vs.**
  Conservative strategy

- **DAM**

  - short-term decision tree and a long-term Markov structure

  - equation 1: estimate risk of combined endpoint (CVD/MI) during the index hospitalisation – **Logistic regression**

  - equation 2: estimate risk of combined endpoint during remainder of trial period – **Weibull regression**

  - equation 3: estimate risk of second composite endpoint following non-fatal MI – **Weibull regression**

  - equation 4: estimate proportion composite endpoints being non fatal – **Logistic regression**

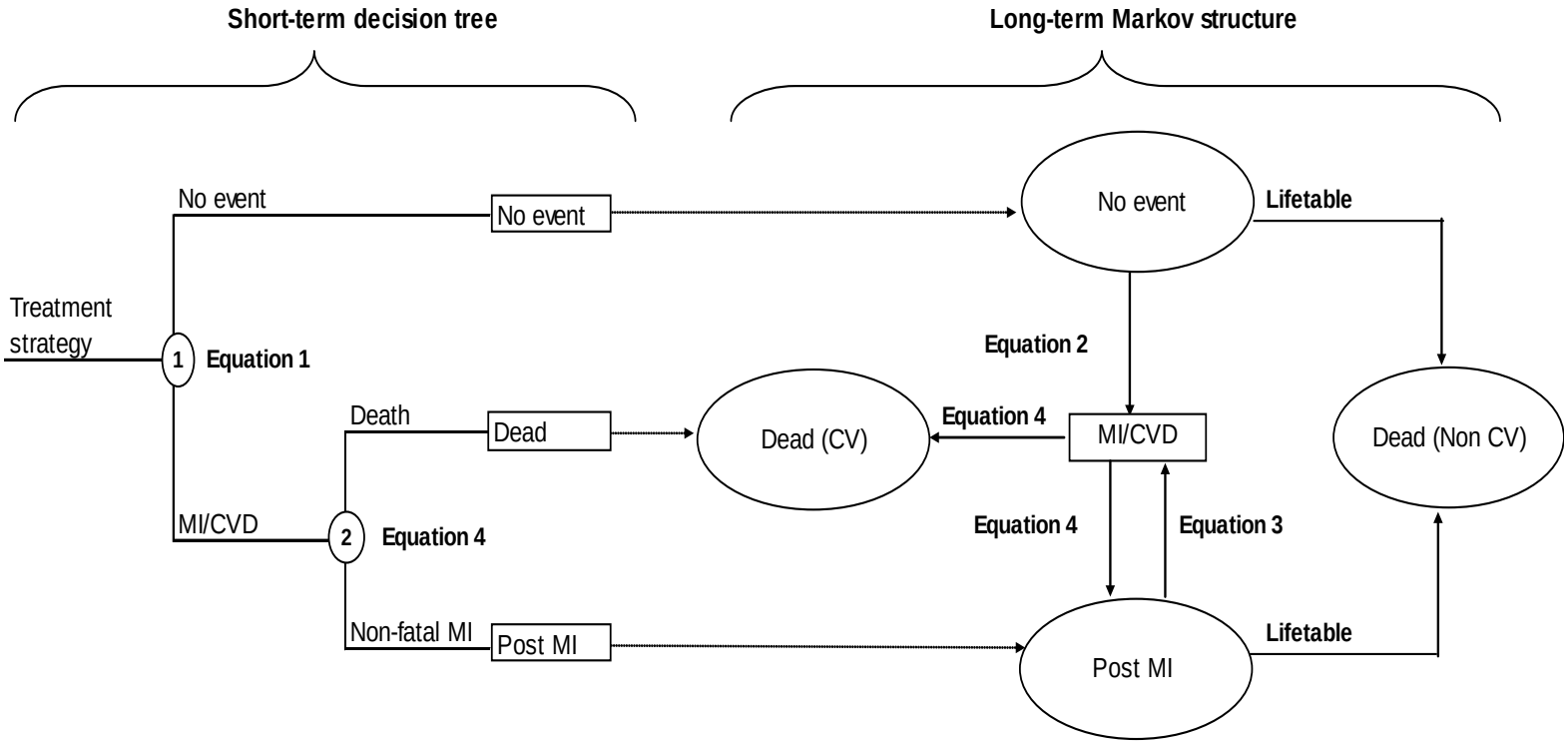
Motivating Example: The RITA 3 Trial

- **DAM (cont.)**

  - Costs: **two standard OLS regressions** used to determine mean costs during the index hospitalisation and for the remainder of the trial

  - HRQoL: **standard OLS**: estimate mean HRQoL of patients with different risk profiles at randomization; **Linear Mixed model**: estimate changes in HRQoL after randomization

Motivating Example: The RITA 3 Trial



Henriksson et al (2008)

Results

Equation 1: log-odds ratio of composite endpoint (CVD/MI) during index hospitalisation

Logistic regression

CCIndex	Stata - NHM			R - NHM			WinBugs** - NHM				WinBugs** - HM			
Covariate	coef.*	std. err.	Pr(>|z|)	coef.*	std. err.	Pr(>|z|)	mean*	std. dev.	95% CrI		mean*	std. dev.	95% CrI	
Fixed Effects														
Treat	0.417	0.288	0.148	0.417	0.288	0.148	0.425	0.294	-0.143	1.008	0.386	0.308	-0.223	0.980
Age	0.549	0.161	0.001	0.549	0.161	0.001	0.554	0.162	0.243	0.874	0.576	0.165	0.260	0.913
Angina	0.636	0.284	0.025	0.636	0.284	0.025	0.635	0.287	0.068	1.195	0.627	0.286	0.064	1.202
Constant	-4.622	0.334	0.000	-4.622	0.334	0.000	-4.671	0.338	-5.355	-4.039	-4.841	0.392	-5.680	-4.159
Random Effects														
σ_{Treat}	-	-	-	-	-	-	-	-	-	-	0.198	0.244	0.012	0.866
σ_{Cnst}	-	-	-	-	-	-	-	-	-	-	0.432	0.370	0.011	1.176
ρ_{Treat_Cnst}	-	-	-	-	-	-	-	-	-	-		0.00142		

*Values in log odds ratios

**5,000 iterations and a 2,000 iteration burn-in period

Centre specific random effects for 5 centres

Logistic regression

CCIndex		WinBugs** - HM			
Centre		mean	std. dev.	95% CrI	
Random Effects					
centre 2	$u_{1j\ -\ Treat}$	-0.019	0.305	-0.682	0.555
	$u_{0j\ -\ Cnst}$	-0.103	0.529	-1.365	0.901
centre 11	$u_{1j\ -\ Treat}$	0.092	0.292	-0.289	0.954
	$u_{0j\ -\ Cnst}$	0.057	0.361	-0.710	0.886
centre 23	$u_{1j\ -\ Treat}$	-0.077	0.317	-0.928	0.391
	$u_{0j\ -\ Cnst}$	-0.146	0.436	-1.267	0.643
centre 37	$u_{1j\ -\ Treat}$	-0.030	0.261	-0.686	0.504
	$u_{0j\ -\ Cnst}$	0.122	0.390	-0.585	1.103
centre 40	$u_{1j\ -\ Treat}$	-0.024	0.243	-0.641	0.463
	$u_{0j\ -\ Cnst}$	0.382	0.490	-0.196	1.517

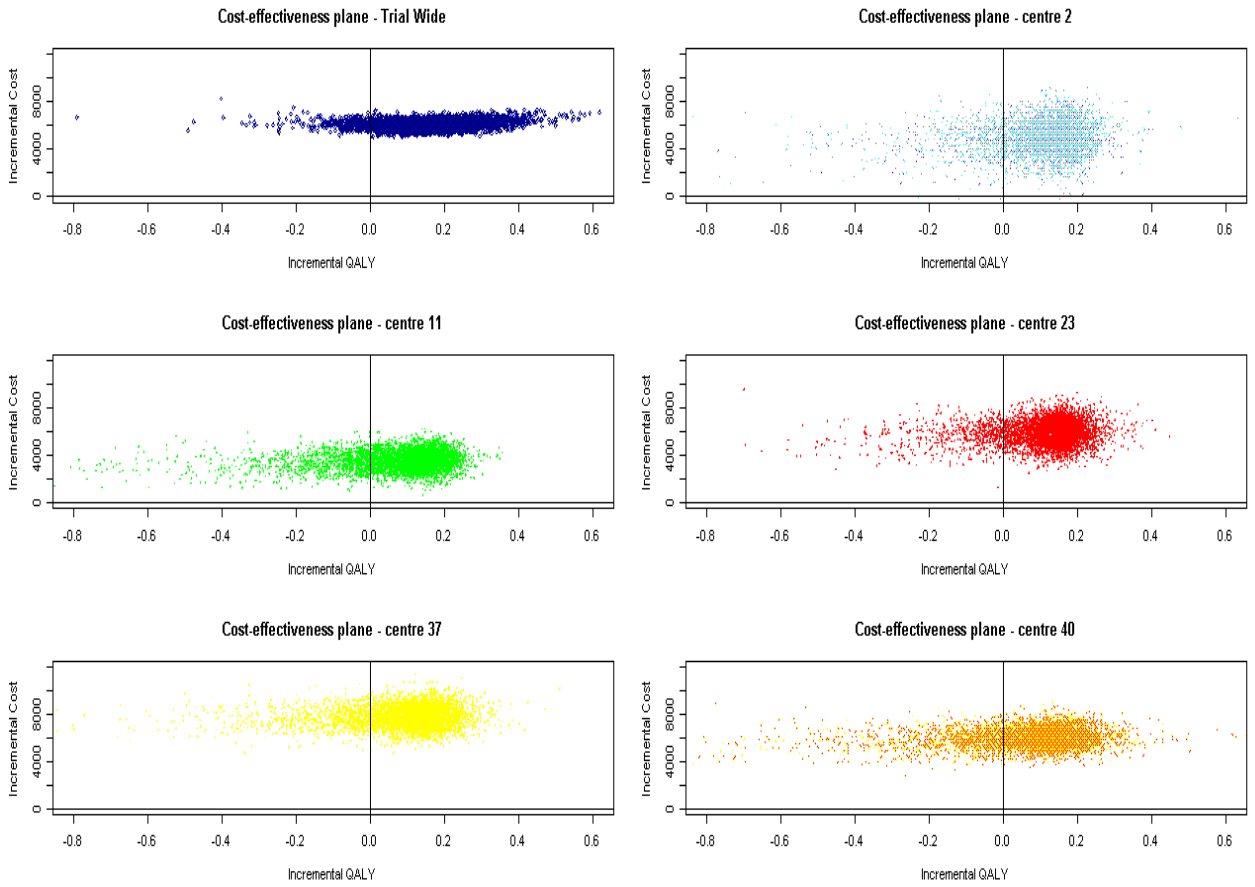
**5,000 iterations and a 2,000 iteration burn-in period

Pedro Saramago

THE UNIVERSITY of York CHE Centre For Health Economics

Results

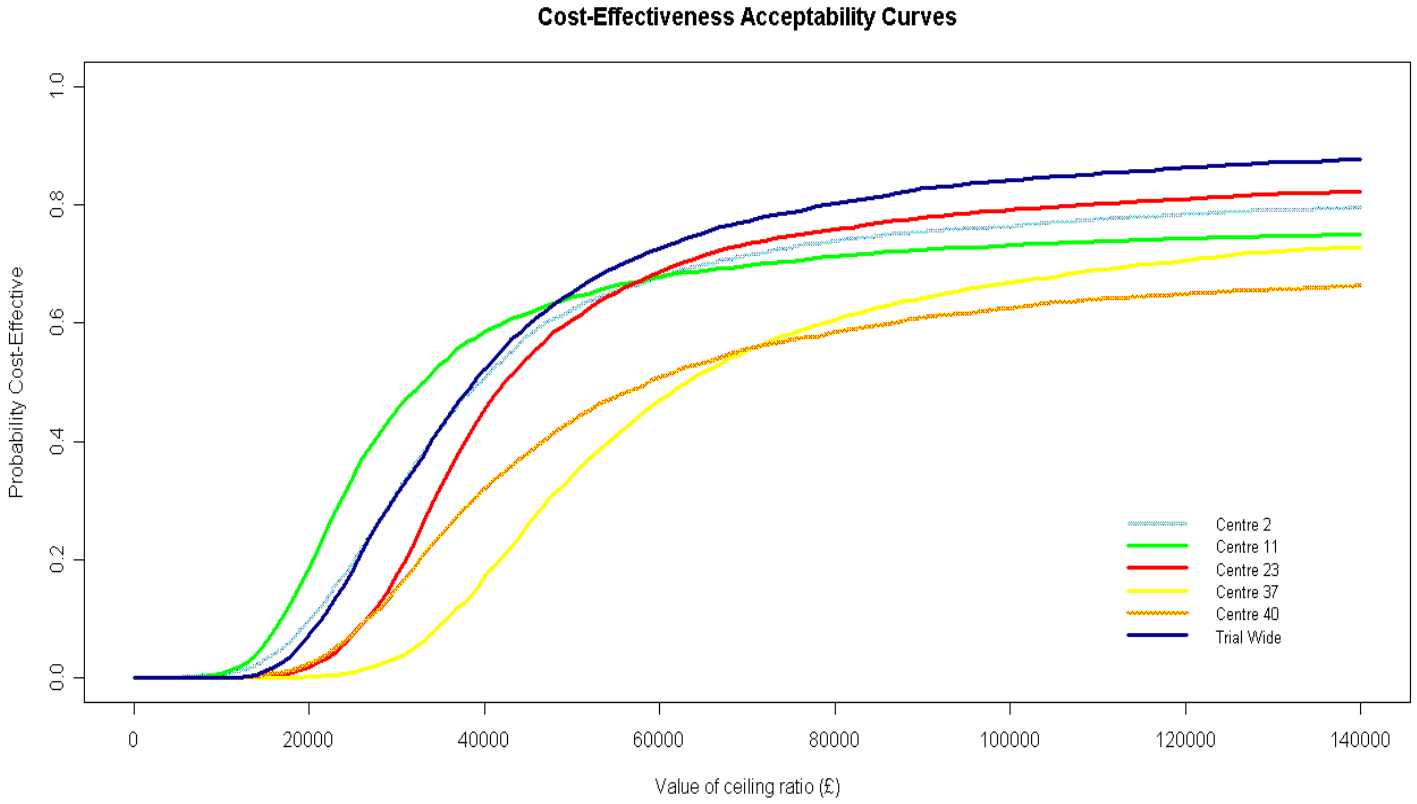
CEPs with trial wide results and centre-specific results



Centre-specific CEPs show higher variability in mean differential cost and mean differential QALY estimates compared to the trial wide results

Results

- Great variability across centres in CE for given values of the threshold, λ



Conclusions

- **Bayesian hierarchical modelling** - ideal to estimate cluster-specific parameters for use in DAMs where IPD from multilocation trial is available.

- Used both **frequentist (two-stages)** and **Bayesian approach (one-stage)** in the analysis, although the latter looks more promising and appropriate from the methodological point of view

- **Extensions:** this framework can be extended to facilitate statistical evidence synthesis, where have multiple sources of evidence to inform estimation of a particular model parameter

- Contact: **prsg500@york.ac.uk**

Pedro Saramago