

Contents

Preface	xi
List of examples	xiii
1 Introduction	1
1.1 What are Bayesian methods?	1
1.2 What do we mean by 'health-care evaluation'?	2
1.3 A Bayesian approach to evaluation	3
1.4 The aim of this book and the intended audience	3
1.5 Structure of the book	4
2 Basic Concepts from Traditional Statistical Analysis	9
2.1 Probability	10
2.1.1 What is probability?	10
2.1.2 Odds and log-odds	12
2.1.3 Bayes theorem for simple events	13
2.2 Random variables, parameters and likelihood	14
2.2.1 Random variables and their distributions	14
2.2.2 Expectation, variance, covariance and correlation	16
2.2.3 Parametric distributions and conditional independence	17
2.2.4 Likelihoods	18
2.3 The normal distribution	20
2.4 Normal likelihoods	22
2.4.1 Normal approximations for binary data	23
2.4.2 Normal likelihoods for survival data	27
2.4.3 Normal likelihoods for count responses	30
2.4.4 Normal likelihoods for continuous responses	31
2.5 Classical inference	31
2.6 A catalogue of useful distributions*	34
2.6.1 Binomial and Bernoulli	34
2.6.2 Poisson	35
2.6.3 Beta	36
2.6.4 Uniform	38
2.6.5 Gamma	39
2.6.6 Root-inverse-gamma	40
2.6.7 Half-normal	41

2.6.8	Log-normal	42
2.6.9	Student's t	43
2.6.10	Bivariate normal	44
2.7	Key points	46
	Exercises	46

3 An Overview of the Bayesian Approach 49

3.1	Subjectivity and context	49
3.2	Bayes theorem for two hypotheses	51
3.3	Comparing simple hypotheses: likelihood ratios and Bayes factors	54
3.4	Exchangeability and parametric modelling*	56
3.5	Bayes theorem for general quantities	57
3.6	Bayesian analysis with binary data	57
3.6.1	Binary data with a discrete prior distribution	58
3.6.2	Conjugate analysis for binary data	59
3.7	Bayesian analysis with normal distributions	62
3.8	Point estimation, interval estimation and interval hypotheses	64
3.9	The prior distribution	73
3.10	How to use Bayes theorem to interpret trial results	74
3.11	The 'credibility' of significant trial results*	75
3.12	Sequential use of Bayes theorem*	79
3.13	Predictions	80
3.13.1	Predictions in the Bayesian framework	80
3.13.2	Predictions for binary data*	81
3.13.3	Predictions for normal data	83
3.14	Decision-making	85
3.15	Design	90
3.16	Use of historical data	90
3.17	Multiplicity, exchangeability and hierarchical models	91
3.18	Dealing with nuisance parameters*	100
3.18.1	Alternative methods for eliminating nuisance parameters*	100
3.18.2	Profile likelihood in a hierarchical model*	102
3.19	Computational issues	102
3.19.1	Monte Carlo methods	103
3.19.2	Markov chain Monte Carlo methods	105
3.19.3	WinBUGS	107
3.20	Schools of Bayesians	112
3.21	A Bayesian checklist	113
3.22	Further reading	115
3.23	Key points	116
	Exercises	117

4 Comparison of Alternative Approaches to Inference 121

4.1	A structure for alternative approaches	121
4.2	Conventional statistical methods used in health-care evaluation	122
4.3	The likelihood principle, sequential analysis and types of error	124
4.3.1	The likelihood principle	124
4.3.2	Sequential analysis	126
4.3.3	Type I and Type II error	127
4.4	P -values and Bayes factors*	127

4.4.1	Criticism of P -values	127
4.4.2	Bayes factors as an alternative to P -values: simple hypotheses	128
4.4.3	Bayes factors as an alternative to P -values: composite hypotheses	130
4.4.4	Bayes factors in preference studies	133
4.4.5	Lindley's paradox	135
4.5	Key points	136
	Exercises	136

5 Prior Distributions

139

5.1	Introduction	139
5.2	Elicitation of opinion: a brief review	140
5.2.1	Background to elicitation	140
5.2.2	Elicitation techniques	141
5.2.3	Elicitation from multiple experts	142
5.3	Critique of prior elicitation	147
5.4	Summary of external evidence*	148
5.5	Default priors	157
5.5.1	'Non-informative' or 'reference' priors:	157
5.5.2	'Sceptical' priors	158
5.5.3	'Enthusiastic' priors	160
5.5.4	Priors with a point mass at the null hypothesis (<i>'lump-and-smear' priors</i>)*	161
5.6	Sensitivity analysis and 'robust' priors	165
5.7	Hierarchical priors	167
5.7.1	The judgement of exchangeability	167
5.7.2	The form for the random-effects distribution	168
5.7.3	The prior for the standard deviation of the random effects*	168
5.8	Empirical criticism of priors	174
5.9	Key points	176
	Exercises	177

6 Randomised Controlled Trials

181

6.1	Introduction	181
6.2	Use of a loss function: is a clinical trial for inference or decision?	182
6.3	Specification of null hypotheses	184
6.4	Ethics and randomisation: a brief review	187
6.4.1	Is randomisation necessary?	187
6.4.2	When is it ethical to randomise?	187
6.5	Sample size of non-sequential trials	189
6.5.1	Alternative approaches to sample-size assessment	189
6.5.2	'Classical power': hybrid classical-Bayesian methods assuming normality	193
6.5.3	'Bayesian power'	194
6.5.4	Adjusting formulae for different hypotheses	196
6.5.5	Predictive distribution of power and necessary sample size	201
6.6	Monitoring of sequential trials	202
6.6.1	Introduction	202
6.6.2	Monitoring using the posterior distribution	204
6.6.3	Monitoring using predictions: 'interim power'	211
6.6.4	Monitoring using a formal loss function	220

6.6.5	Frequentist properties of sequential Bayesian methods	221
6.6.6	Bayesian methods and data monitoring committees	222
6.7	The role of 'scepticism' in confirmatory studies	224
6.8	Multiplicity in randomised trials	227
6.8.1	Subset analysis	227
6.8.2	Multi-centre analysis	227
6.8.3	Cluster randomisation	227
6.8.4	Multiple endpoints and treatments	228
6.9	Using historical controls*	228
6.10	Data-dependent allocation	235
6.11	Trial designs other than two parallel groups	237
6.12	Other aspects of drug development	242
6.13	Further reading	244
6.14	Key points	245
	Exercises	247

7 Observational Studies 251

7.1	Introduction	251
7.2	Alternative study designs	252
7.3	Explicit modelling of biases	253
7.4	Institutional comparisons	258
7.5	Key points	262
	Exercises	263

8 Evidence Synthesis 267

8.1	Introduction	267
8.2	'Standard' meta-analysis	268
8.2.1	A Bayesian perspective	268
8.2.2	Some delicate issues in Bayesian meta-analysis	274
8.2.3	The relationship between treatment effect and underlying risk	278
8.3	Indirect comparison studies	282
8.4	Generalised evidence synthesis	285
8.5	Further reading	298
8.6	Key points	299
	Exercises	299

9 Cost-effectiveness, Policy-Making and Regulation 305

9.1	Introduction	305
9.2	Contexts	306
9.3	'Standard' cost-effectiveness analysis without uncertainty	308
9.4	'Two-stage' and integrated approaches to uncertainty in cost-effectiveness modelling	310
9.5	Probabilistic analysis of sensitivity to uncertainty about parameters: two-stage approach	312
9.6	Cost-effectiveness analyses of a single study: integrated approach	315
9.7	Levels of uncertainty in cost-effectiveness models	320
9.8	Complex cost-effectiveness models	322
9.8.1	Discrete-time, discrete-state Markov models	322
9.8.2	Micro-simulation in cost-effectiveness models	323

9.8.3	Micro-simulation and probabilistic sensitivity analysis	324
9.8.4	Comprehensive decision modelling	328
9.9	Simultaneous evidence synthesis and complex cost-effectiveness modelling	329
9.9.1	Generalised meta-analysis of evidence	329
9.9.2	Comparison of integrated Bayesian and two-stage approach	335
9.10	Cost-effectiveness of carrying out research: payback models	335
9.10.1	Research planning in the public sector	335
9.10.2	Research planning in the pharmaceutical industry	336
9.10.3	Value of information	337
9.11	Decision theory in cost-effectiveness analysis, regulation and policy	341
9.12	Regulation and health policy	343
9.12.1	The regulatory context	343
9.12.2	Regulation of pharmaceuticals	343
9.12.3	Regulation of medical devices	344
9.13	Conclusions	344
9.14	Key points	345
	Exercises	345
10	Conclusions and Implications for Future Research	349
10.1	Introduction	349
10.2	General advantages and problems of a Bayesian approach	349
10.3	Future research and development	350
A	Websites and Software	353
A.1	The site for this book	353
A.2	Bayesian methods in health-care evaluation	353
A.3	Bayesian software	354
A.4	General Bayesian sites	355
	References	357
	Index	381