Subgroup analyses in cost-effectiveness to support health technology assessments

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PSI Journal Club

Nov 2014

Acknowledgements

MAIN PAPER

Pharmaceutical Statistics

(wileyonlinelibrary.com) DOI: 10.1002/pst.1626

Published online 15 June 2014 in Wiley Online Library

Subgroup analyses in cost-effectiveness analyses to support health technology assessments

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'Success' in drug development is bringing to patients a new medicine that has an acceptable benefit–risk profile and that is also cost-effective. Cost-effectiveness means that the incremental clinical benefit is deemed worth paying for by a healthcare system, and it has an important role in enabling manufacturers to obtain new medicines to patients as soon as possible following regulatory approval. Subgroup analyses are increasingly being utilised by decision-makers in the determination of the cost-effectiveness of new medicines when making recommendations. This paper highlights the statistical considerations when using subgroup analyses to support cost-effectiveness for a health technology assessment. The key principles recommended for subgroup analyses supporting clinical effectiveness published by Paget *et al.* are evaluated with respect to subgroup analyses supporting cost-effectiveness. A health technology assessment case study is included to highlight the importance of subgroup analyses when incorporated into cost-effectiveness analyses. In summary, we recommend planning subgroup analyses for cost-effectiveness analyses early in the drug development process and adhering to good statistical principles when using subgroup analyses in this context. In particular, we consider it important to provide transparency in how subgroups are defined, be able to demonstrate the robustness of the subgroup results and be able to quantify the uncertainty in the subgroup analyses of cost-effectiveness.

Disclaimer

- The views expressed herein represent those of the presenter and do not necessarily represent the views or practices of Amgen.

Overview

- Introduction
- Statistical considerations in cost-effectiveness analyses
- Guiding principles for subgroups in cost-effectiveness
- Example case study
- Discussion and conclusions

Introduction

- “Health technology assessment (HTA) is a form of policy research that examines the short-term and long-term social consequences (e.g. societal, clinical, economic, ethical and legal) of the application of technology” (Banta D)
- Cost-effectiveness analysis (CEA) seeks to identify technologies that if funded, maximise total population health

Introduction (cont)

- Subgroup analyses in CEA help to understand key drivers of CE, quantify the uncertainty and extent of heterogeneity
- Many national pharmacoeconomic guidance's provide recommendations on how to assess patient heterogeneity but there is no consensus on which specific methods are most appropriate

Introduction (cont)

MAIN PAPER

Pharmaceutical Statistics

(wileyonlinelibrary.com) DOI: 10.1002/pst.531

Published online 5 December 2011 in Wiley Online Library

Subgroup analyses of clinical effectiveness to support health technology assessments

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Subgroup analysis is an integral part of access and reimbursement dossiers, in particular health technology assessment (HTA), and their HTA recommendations are often limited to subpopulations. HTA recommendations for subpopulations are not always clear and without controversies. In this paper, we review several HTA guidelines regarding subgroup analyses. We describe good statistical principles for subgroup analyses of clinical effectiveness to support HTAs and include case examples where HTA recommendations were given to subpopulations only. Unlike regulatory submissions, pharmaceutical statisticians in most companies have had limited involvement in the planning, design and preparation of HTA/payers submissions. We hope to change this by highlighting how pharmaceutical statisticians should contribute to payers' submissions. This includes early engagement in reimbursement strategy discussions to influence the design, analysis and interpretation of phase III randomized clinical trials as well as meta-analyses/network meta-analyses. The focus on this paper is on subgroup analyses relating to clinical effectiveness as we believe this is the first key step of statistical involvement and influence in the preparation of HTA and reimbursement submissions.

Principles and best practices for subgroup analyses (Paget et al)

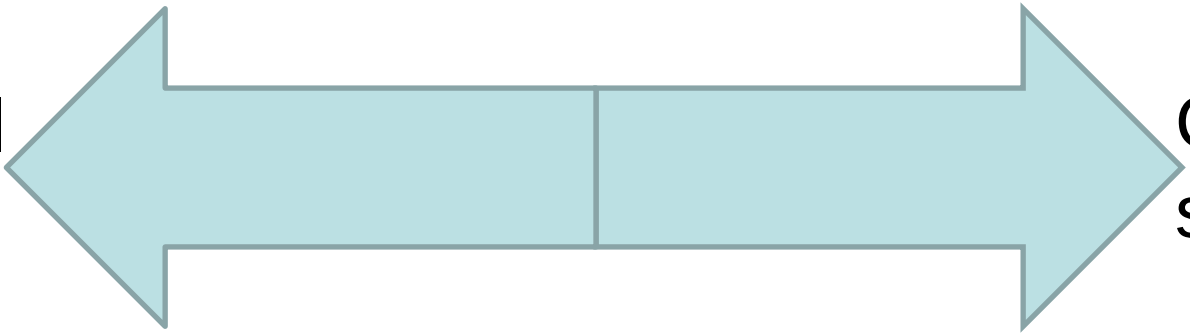
- Subgroups pre-specification & definition
- Subgroup by treatment interaction
- Multiplicity issues
- Sensitivity analyses
- Replication
- Source of evidence
- Presenting and reporting subgroup results

Statistical considerations in CEA

Random variation?

Uncertainty ?

Generalisability ?

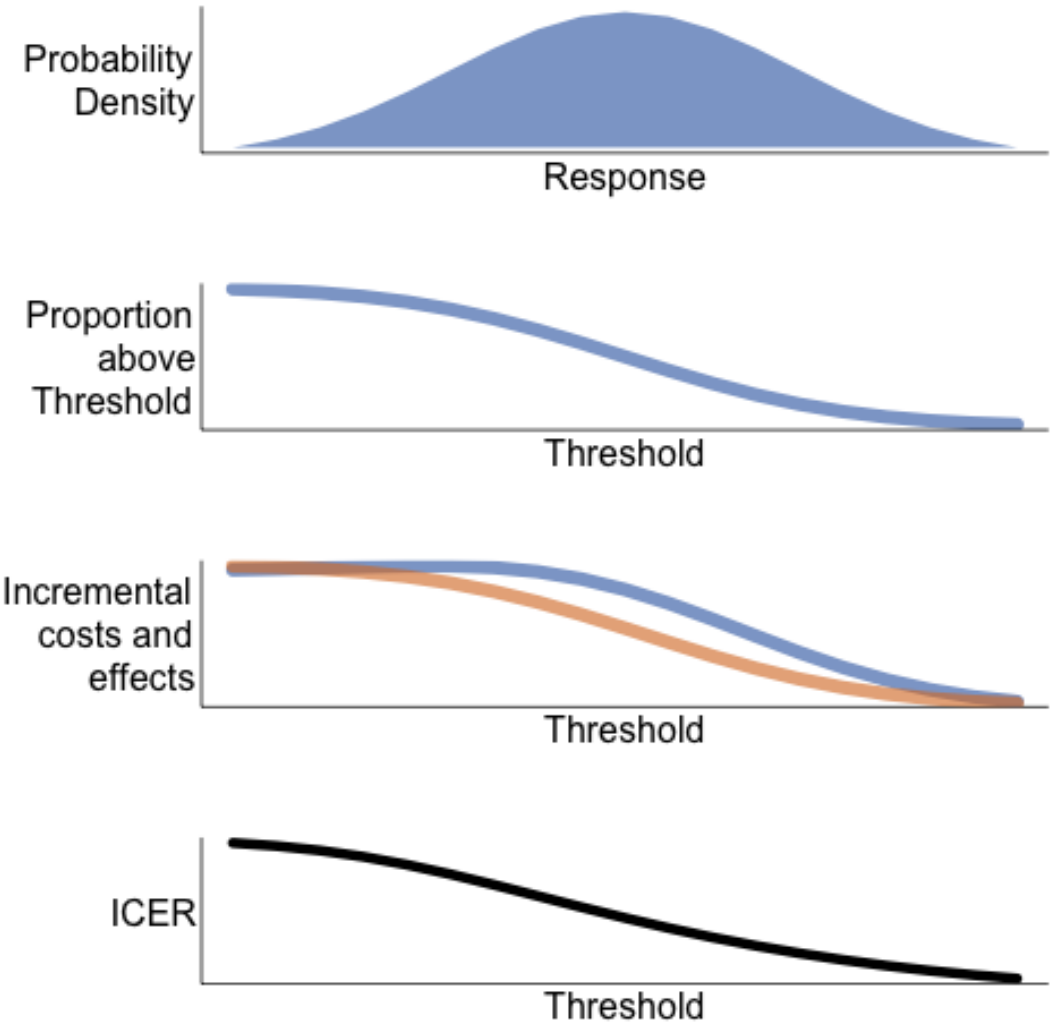


Subgroup definition ?

Number of subgroups ?

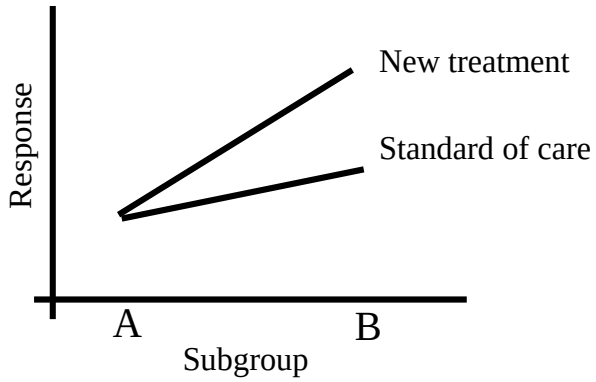
Cost to identify subgroup ?

When is a subgroup cost-effective?

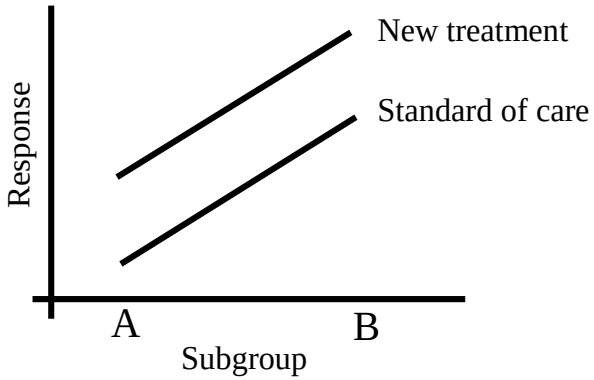


Subgroup effects can be predictive or prognostic

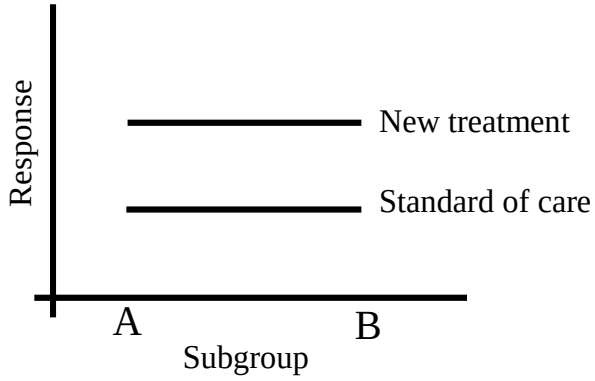
Predictive subgroup



Prognostic subgroup



No subgroup effect



Concluding a subgroup is predictive can depend on the scale used to measure the treatment effect

Subgroups for regulatory vs reimbursement

Regulatory

- Assess consistency of treatment effects in individual subgroup factors
- Balance of benefit and risks

Reimbursement

- Assess total budget impact of multiple subgroup factors considered jointly (optimise healthcare spend under constraints)
- Balance benefit, risks and costs

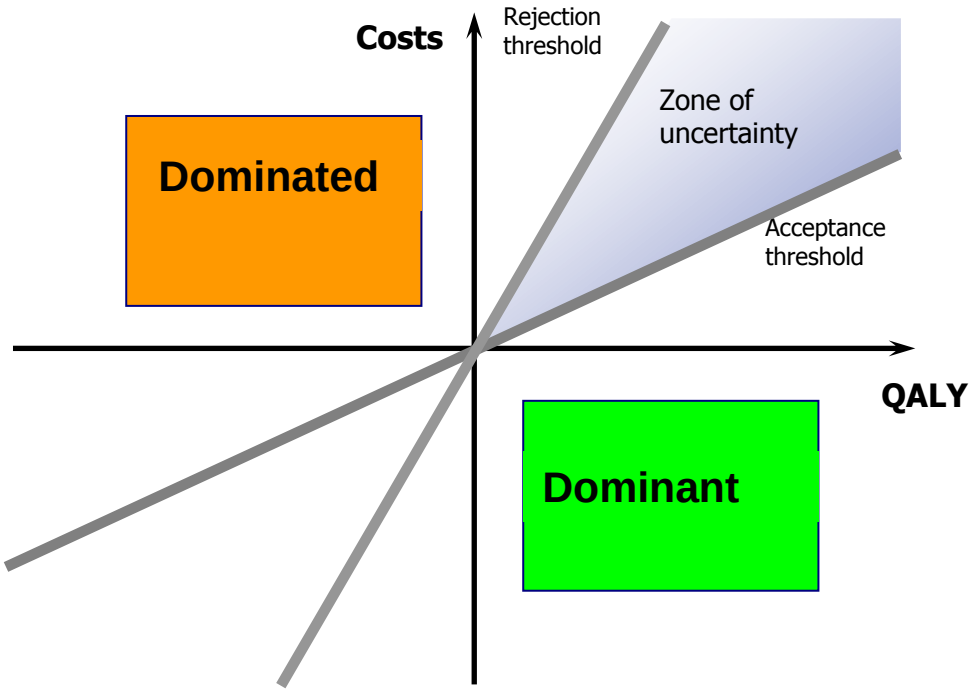
Both concerned with ‘optimism’ bias, biological plausibility, credibility, and relevance to clinical practice

Planning subgroups in confirmatory trials

- Consider for both regulators and payers
- Regulatory (EMA draft guideline)
  - Assessing consistency, biological plausibility, replication, pre-specification and multiplicity
- Payers (EUnetHTA, NICE methods)
  - Absolute effects (scale), biological and economic plausibility, pre-specification, quantify heterogeneity (estimation)

Useful approaches in subgroup analyses for CEA

- Bayesian analysis to shrink subgroup results towards average population
- Probabilistic sensitivity analyses (PSA)



Guiding principles for cost-effectiveness subgroup analyses

Clinical effectiveness	Cost-effectiveness
Sensitivity analyses	Extremely important
Presenting and reporting	Transparency
Replication	Important
Source of evidence	All data sources
Pre-specification of subgroups	Desirable
Multiplicity issues	Less important
Subgroup by trt interaction	Less important

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Example case study

Table I. Comparison of cost-effectiveness assessments.

	TA111 (Nov 2006)		TA217 (March 2011)	
Issue	Manufacturers	NICE	Manufacturers	NICE
Prespecified subgroups	No	Retrospective analysis suggested incremental cognitive benefit in more severely impaired patients	No, clinical effectiveness in subgroups not performed	No, clinical effectiveness in subgroups not assessed.
Studies included for clinical effectiveness	RCTs + OL and observational studies	RCTs, including some with doses not used in clinical setting	RCTs + OL & observational studies	RCTs
Assumptions on:				
Cost	100% of costs of care met by NHS	Only 70% of costs of full-time care would be met by the NHS	All costs included	Excluded costs to individual of institutional care
Discontinuation		Discontinuation of treatment not accounted for	Discontinuation assessed in sensitivity analyses	Discontinuation rate = 4% per month
Mortality	AHEAD risk equation (galantamine)	Annual mortality rate = 11.2%	Survival = 4.6 life years (moderate cohort)	Survival = 3.6 life years (moderate cohort)
Time horizon	5 years (donepezil and rivastigmine), 10 years (galantamine) and 2 years (memantine)	5 years, also 2 years for memantine	Lifetime (donepezil), 5 years (others)	20-year time horizon (mild–moderate)

Discussions and conclusions

- Subgroup analyses are important in CEA
- Many subgroup analyses guiding principles for clinical effectiveness apply to CEA
- Importance of documenting methods, assumptions and sensitivity analyses
- Statisticians and health economics together should plan analytical strategies for CEA early in the drug development process

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