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Methods to Acknowledge Patient Heterogeneity in Economic Evaluation: A Review of the Methods Literature

Shields G[1], Bullement A[2], Clarkson P[3], Wilberforce M[4], Farragher T[5], Verma A[5], Davies L[1]

[1]Manchester Centre for Health Economics, The University of Manchester
[2]Health Economics and Decision Science, School of Health and Related Research, University of Sheffield
[3]Social Care and Society, Division of Nursing, Midwifery and Social Work, University of Manchester
[4]Social Policy Research Unit, Department of Social Policy & Social Work, University of York
[5]The Epidemiology and Public Health Group, University of Manchester

Background

- Economic evaluations commonly apply averages from populations
  - Neglects to consider patient heterogeneity
  - Ignores potentially different results across subpopulations [1]
- Most national pharmacoeconomic guidelines discuss patient heterogeneity, however they lack specific details on recommended methods [3]
- A review found a minority (19%) of cost-effectiveness analyses reported subgroup analyses [4]

Patient heterogeneity is defined as natural variation across people, which can be explained by their characteristics [1–3]

Demographics

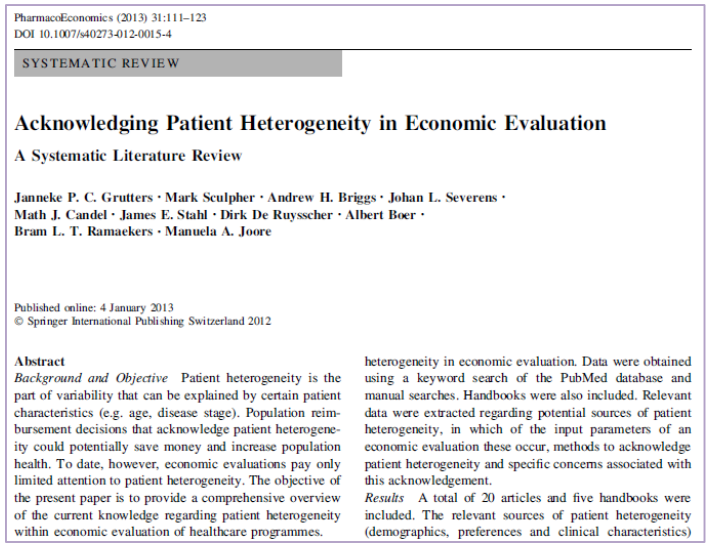
Clinical characteristics

Preferences

[1] Grutters JPC, Sculpher M, Briggs AH, Severens JL, Candel MJ, Stahl JE, De Ruysscher D, Boer A, Ramaekers BLT, Joore MA (2013) Acknowledging Patient Heterogeneity in Economic Evaluation. Pharmacoeconomics 31:111–123.
[2] Briggs A, Sculpher M, Claxton K (2006) Decision modelling for health economic evaluation. Oxford university press.
[3] Ramaekers BLT, Joore MA, Grutters JPC (2013) How Should We Deal with Patient Heterogeneity in Economic Evaluation: A Systematic Review of National Pharmacoeconomic Guidelines. Value Heal 16:855–862.
[4] Lavelle TA, Kent DM, Lundquist CM, Thorat T, Cohen JT, Wong JB, et al. Patient Variability Seldom Assessed in Cost-effectiveness Studies. Med Decis Mak. 2018 May 1;38(4):487–94.

Background

- An existing review of methods to acknowledge patient heterogeneity in economic evaluations is available (identified literature up until 2011) [1]
  - Regression techniques (e.g., for model parameters, to identify subgroups)
  - Model parameters (i.e., different parameters by subgroup)
  - Modelling techniques (e.g., patient-level simulation)
  - Techniques to assess the value of acknowledging heterogeneity



PharmacoEconomics (2013) 31:111–123
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SYSTEMATIC REVIEW

Acknowledging Patient Heterogeneity in Economic Evaluation

A Systematic Literature Review

Janneke P. C. Grutters · Mark Sculpher · Andrew H. Briggs · Johan L. Severens · Math J. Candel · James E. Stahl · Dirk De Ruysscher · Albert Boer · Bram L. T. Ramaekers · Manuela A. Joore

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Abstract
Background and Objective Patient heterogeneity is the part of variability that can be explained by certain patient characteristics (e.g. age, disease stage). Population reimbursement decisions that acknowledge patient heterogeneity could potentially save money and increase population health. To date, however, economic evaluations pay only limited attention to patient heterogeneity. The objective of the present paper is to provide a comprehensive overview of the current knowledge regarding patient heterogeneity within economic evaluation of healthcare programmes.

heterogeneity in economic evaluation. Data were obtained using a keyword search of the PubMed database and manual searches. Handbooks were also included. Relevant data were extracted regarding potential sources of patient heterogeneity, in which of the input parameters of an economic evaluation these occur, methods to acknowledge patient heterogeneity and specific concerns associated with this acknowledgement.
Results A total of 20 articles and five handbooks were included. The relevant sources of patient heterogeneity (demographics, preferences and clinical characteristics)

Objective: To identify recent advances in methods for acknowledging patient heterogeneity in economic evaluations and to provide an overview of these methods

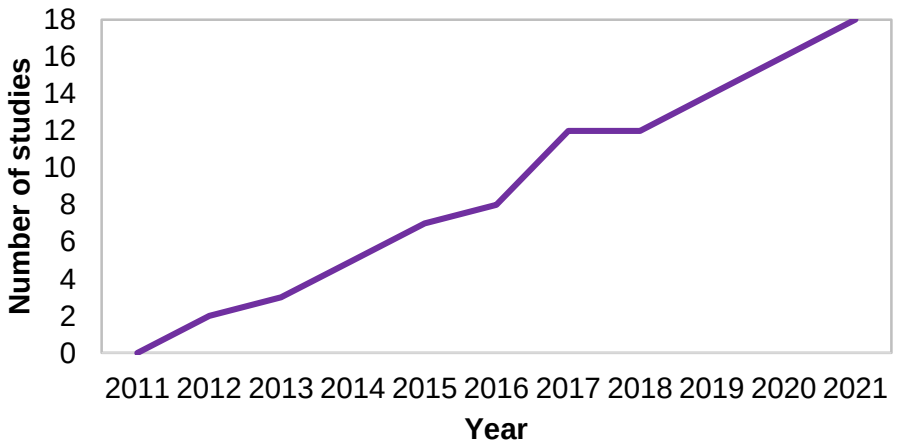
[1] Grutters JPC, Sculpher M, Briggs AH, Severens JL, Candel MJ, Stahl JE, De Ruysscher D, Boer A, Ramaekers BLT, Joore MA (2013) Acknowledging Patient Heterogeneity in Economic Evaluation. Pharmacoeconomics 31:111–123 .

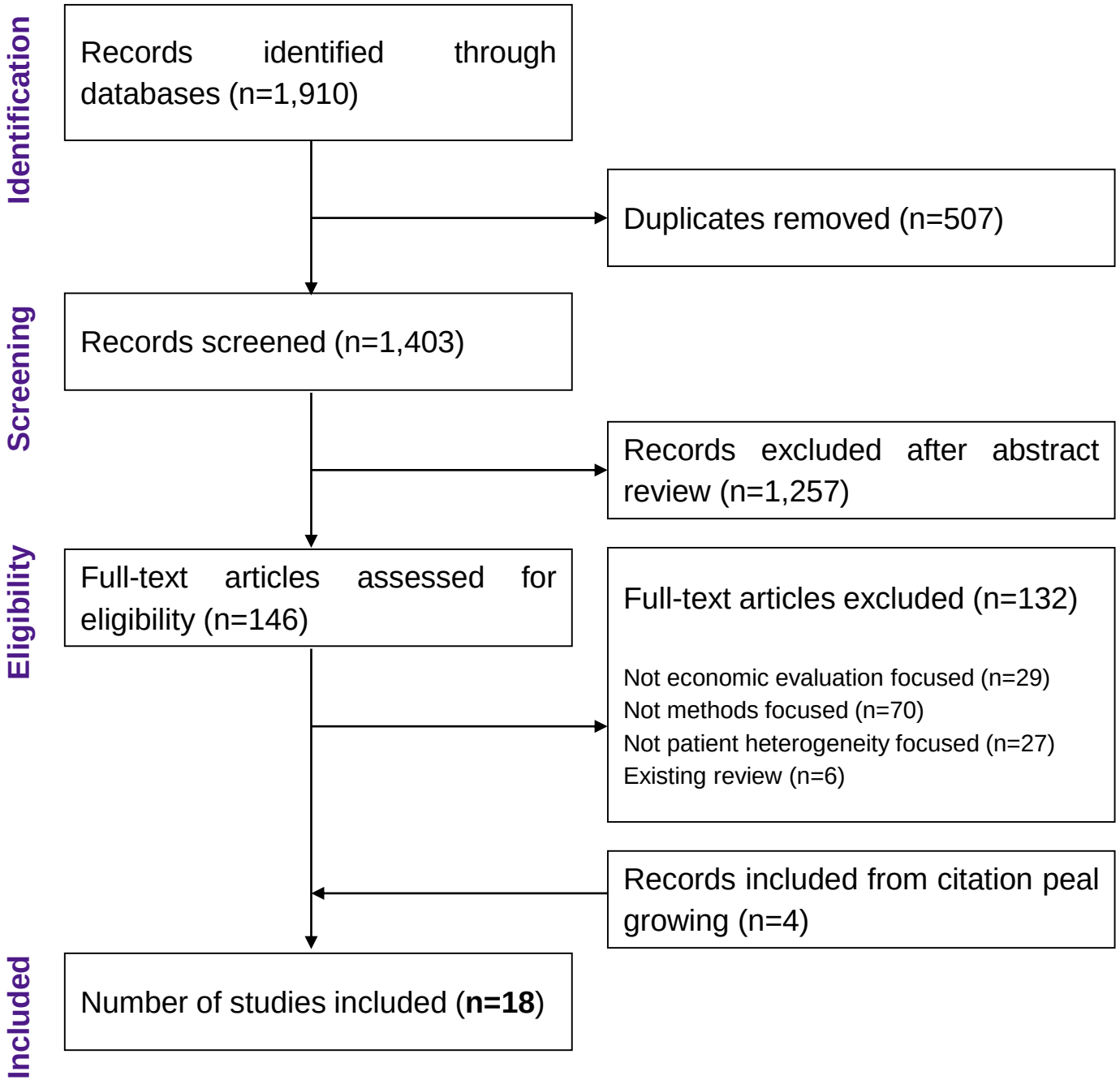
Methods

Focus			Other		
Patient heterogeneity	Economic evaluation	Methods objective	Date	Publication type	Language
• Papers were required to consider patient heterogeneity	• Papers needed to focus on economic evaluation in healthcare (i.e. the comparative analysis of two or more intervention in terms of their costs and consequences) • Trial or modelling based studies were included	• Papers needed to have an explicit methodological objective. The objective/aim/research question and/or title needed to be labelled as 'methodology' or 'methods', or alternatively needed to use closely related language (e.g., to 'propose' or 'develop')	• 1st January 2011 - current	• Full-text articles- reporting a new method or extension to an existing method	• English language

Results

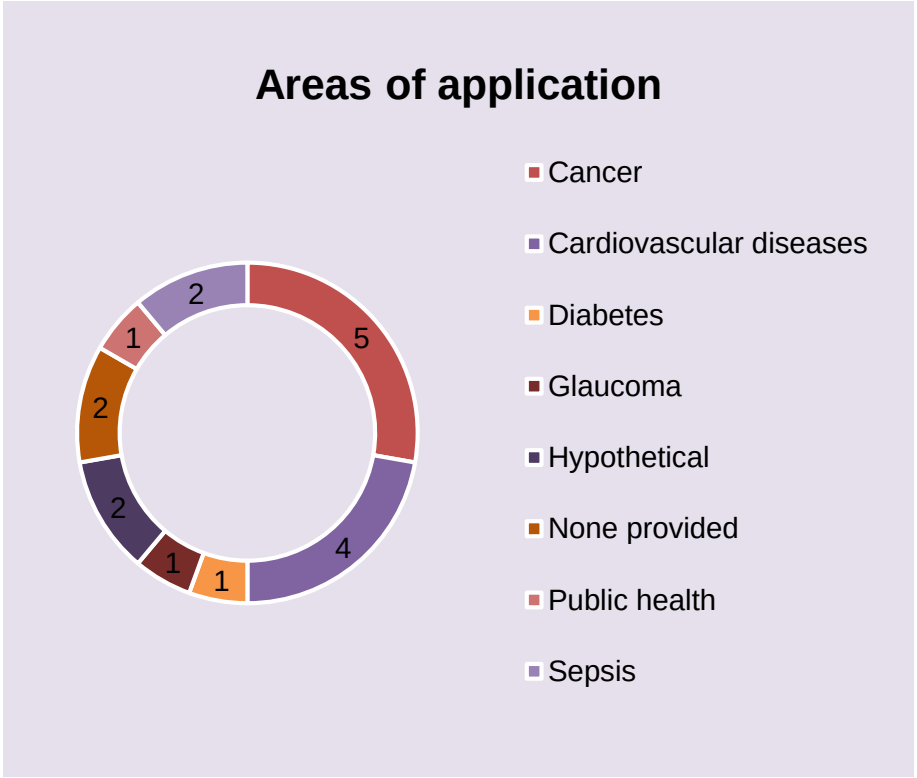
- 18 studies included in the review
  - First authors typically from institutions in a few countries the Netherlands (7), USA (5) and UK (3)
  - Growing evidence base





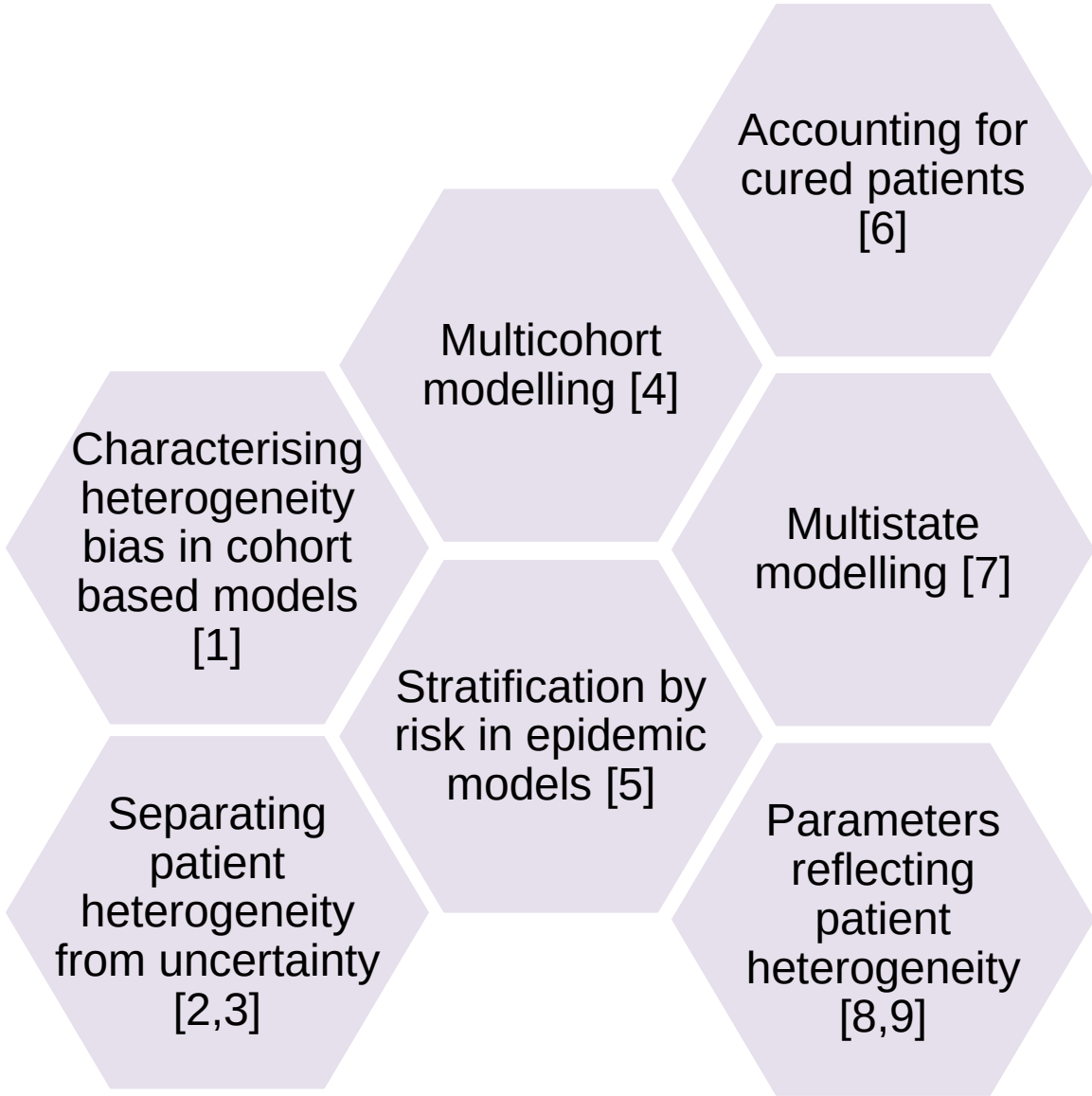
Results

- Authors have considered a variety of methods to acknowledge patient heterogeneity
  - ➢ Aims, methodologies and sources of data were varied
- Papers commonly used case studies to illustrate methods
- Papers concentrated on three key areas
  1. Approaches to modelling
  2. Exploring value
  3. Identifying heterogeneity and subsequently reflecting this in cost-effectiveness analysis



Results: Approaches to modelling

- Many papers focused on approaches to modelling, which included:
  - Structures
  - Parameterisation
  - Appropriate sensitivity analysis
- The relevance of applications can differ according to the disease/condition
- In general, there is an acceptance that typical cohort models may not be sufficient when considering patient heterogeneity



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[2] Vemer P, Goossens LMA, Rutten-van Mölken MPMH (2014) Med Decis Mak 34:1048–1058.
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[7] Bongers ML, De Ruysscher D, Oberije C, Lambin P, Uyl-De Groot CA, Coupé VMH (2016) Med Decis Mak 36:86–100.
[8] Welton NJ, Soares MO, Palmer S, Ades AE, Harrison D, Shankar-Hari M, Rowan KM (2015) Med Decis Mak 35:608–621.
[9] Goto D, Shih YCT, Lecomte P, Olson M, Udeze C, Park Y, Mullins CD (2017) Pharmacoeconomics 35:685–695.

Results: Exploring value

Added value of individual-participant level data [1]	Value of heterogeneity for subgroup analysis [2]	Value subgroup policy alternatives [3]	Expected value of individualised care [4]
• Value of individual data versus aggregate data • Benefits foregone when individual level data is unavailable • Estimating expected value of perfect information for subgroups of the population	• Efficiency frontier to guide optimal subgroup definition • Static value (factors associated with heterogeneity using current evidence) and dynamic value (value of acquiring further subgroup evidence)	• Cost-effectiveness metrics reflecting alternative subgroup policy and adoption, with a focus on policy decisions • Estimates loss with respect to efficient diffusion metrics	• Quantifies the benefits lost when decisions are made at a population, rather than an individual, level • Examines feasibility as an additional objective

[1] Saramago P, Espinoza MA, Sutton AJ, Manca A, Claxton K (2019) Appl Health Econ Health Policy 17:273–284.
[2] Espinoza MA, Manca A, Claxton K, Sculpher MJ (2014) Med Decis Mak 34:951–964
[3] Kim DD, Basu A (2017) Med Decis Mak 37:930–941.
[4] Van Gestel A, Grutters J, Schouten J, Webers C, Beckers H, Joore M, Severens J (2012) Value Heal 15:13–21.

Results: Identifying heterogeneity for analysis

- Statistical techniques
  - Bayesian hierarchical models [1], meta-regression techniques [2], regression approaches [3] and subpopulation treatment effect pattern plot [4]
- Machine learning with real-world evidence or observational data
  - Implementation of decision tree and random forest models to identify subgroups [5]
  - Causal forests to estimate heterogeneity in parameters and outcomes [6]
- Preference heterogeneity
  - Choice models to identify the presence of patient heterogeneity with individual-specific parameter estimates used to support cost-effectiveness analysis [7]

[1] Murphy P, Claxton L, Hodgson R, Glynn D, Beresford L, Walton M, Llewellyn A, Palmer S, Dias S (2021) Med Decis Making 41:165–178.
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Results: Challenges and limitations

Reported limitations

10 **Assumption requirements**
- Need to make simplifying assumptions (e.g., varying one aspect of patient heterogeneity at a time, simplifying impact and pathways)

10 **Data availability**
- Challenges around accessing the data required and availability (e.g., is it available from trials) and unmeasured variables

8 **Patient heterogeneity complexity**
- Need to simplify the patient heterogeneity considered (e.g., number of subgroups, interactions between parameters)

7 **Generalisability**
- Patient heterogeneity acknowledgment may not be generalisable to other settings and/or disease areas

4 **Statistical bias**
- Reliance on small samples for some parameters may increase the risk of false negatives. Multiplicity is a potential issue

3 **Underestimating costs**
- Exclusion of heterogeneity related costs (e.g. identification or implementation)

2 **Ethical concerns**
- Papers present potential methods and subsequently researchers/decision makers need to consider the ethics separately

2 **Time requirements**
- Particularly related to modelling studies, acknowledgement of patient heterogeneity can increase computational time

2 **Time-varying factors**
- Patient heterogeneity and the associated impact can change over time, in addition factors can be revealed over time

2 **Implementation concerns**
- Cannot always consider whether subgroups are feasible for decision makers to implement (e.g., number of subgroups, ability to target patients)

Numbers represent the number of studies discussing each limitation (out of the 18 studies identified).

Discussion

- Work in progress!
- There is a growing range of methods available to acknowledge patient heterogeneity in economic evaluation
- Future research is needed to assess whether and how methods are being applied in practice

What is the aim and context (e.g., disease area) of the research?

What are your methods (e.g., trial analysis or modelling study)?

What data are available?

What are the likely limitations?

gemma.shields@manchester.ac.uk