Exploring the impact of Heterogeneity in Economic Evaluations: Current Practice and Implications

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Background and Objectives

> Economic evaluation (EE) is commonly used to inform reimbursement decisions regarding new health technologies. EE for a target populations is often based on average clinical and economic outcomes. However, real-word patients within one target population are heterogeneous. Failing to accommodate for patient heterogeneity in clinical outcomes, health state preference and/or resource use can bias economic outcomes and may lead to suboptimal reimbursement decisions.

> National HTA bodies have published National Pharmacoeconomic Guidelines (NPGs) to provide essential guidance on how EEs must be performed within that jurisdiction, in order to support the reimbursement decision-making. Ramaekers et al. (2013)[1] have conducted the most recent systematic review on how patient heterogeneity is addressed in global NPGs. They concluded that this guidance was general and non-explicit, which therefore limited its usefulness. It is important that NPGs provide specific guidance to addressing heterogeneity in EEs as this will ensure that reimbursement decisions based on specific subgroups are both systematic and transparent.

> This study aims to summarize how national HTA bodies around the world acknowledge patient heterogeneity in their guidance and to explore how manufacturers address patient heterogeneity in HTA submissions for very rare diseases in England & Wales.

Methods

> Updates to how national HTA bodies address patient heterogeneity (Global)
- A targeted literature review of NPGs were analysed to identify any updates since the most recent systematic review in January 2013[1].
- NPGs were sourced from the section of ISPOR's website titled Guidelines Around the World.
- Out of the screened NPGs (n=26), 6 were deemed as having updates on heterogeneity.
- Data was extracted based on updates to how guidelines advised to distinguish between and analytically address patient heterogeneity.

> How patient heterogeneity is addresses by manufacturers for treatments for very rare diseases (England and Wales)
- Manufacturers submit health technology evidence for very rare diseases to NICE for recommendations through the Highly Specialised Technology (HST) route:
- All 15 Highly Specialisation Technology Guidance (HSTGs) by NICE[8] since the start of the program were reviewed.
- Data was extracted based on how the manufacturer may have addressed heterogeneity (decision scope, economic model, sensitivity & scenario analysis).
- Data on how the manufacturer's evidence was critiqued, by the Evidence Review Group (ERG), and final NICE recommendation decisions, were also extracted.
- The information was categorized into the manufacturer's data inputs, how patient heterogeneity was addressed, the economic model and treatment discontinuation rules.

Results

> Updates to how national HTA bodies address patient heterogeneity (Global)

- Since January 2013, 6 NPGs (Australia[2], Canada[3], Finland[4], Ireland[5], New Zealand[6], United States[7]) had updates with explicit and/or implicit implications to how patient heterogeneity should be addressed in HTA submissions. Five out of 6 NPGs had updated regarding analytically acknowledging patient heterogeneity (Table 1).
- The Australian guidance implemented a checklist that lists the possible sources of heterogeneity between study evidence and jurisdictions. They advise that distributions of how each source of heterogeneity impacts the patient heterogeneity must be addressed. This was the only update that is deemed to provide specific guidance that is meaningful for manufacturers.

Table 1. NPGs with updated guidance on how to analytically address patient heterogeneity

Australia[2]	Checklist of the possible sources of heterogeneity has been implemented
Canada[3]	Stratified analyses of subgroups conducted when characteristics that may lead to heterogenous outcomes are identified
Finland[4]	Statistical precision of subgroup estimates should be reflected in uncertainty analysis
Ireland[5]	Under certain contexts, clinical and cost evidence may be published as adjusted values to account for heterogeneity (Ireland)
United States[7]	Patient variability within populations and clinical studies must be considered

> How patient heterogeneity is addressed by manufacturers for treatments for very rare diseases (England and Wales)

- Acknowledging patient heterogeneity in the scope of the decision problem:
  - In 10 (67%) of all 15 HST submissions by manufacturers[8], NICE considers the heterogeneity of clinical benefits in their scope, with pre-specified subgroups that should be analysed in the technology's economic evaluation in 4/10. 7/10 (70%) HSTGs had a manufacturer scope that aligned with NICE's scope in terms of considering heterogeneity of clinical benefits, including 2 HSTs which NICE prespecified subgroup analysis. 3 HSTGs deviated from NICE's scope with 2 claimed due to insufficient evidence to perform the same subgroup analyses as NICE defined in their scopes.
- Addressing patient heterogeneity in economic models:
  - In all HST submissions, Markov models were used for economic evaluation. Fourteen used cohort models and one used individual simulation model (ISM). The manufacturer that exploited the ISM model as it is more appropriate for the modelling of the course of the disease (lipodystrophy). As above, two (13%) HSTGs incorporated more than one (two) patient population(s) into their economic model as NICE prespecified subgroup analysis.
- Addressing patient heterogeneity in scenario analyses: treatment discontinuation rules
  - NICE advises manufacturers to conduct a scenario analysis for treatment continuation rules. Such rules allow for adjusted treatment plans based on differences in treatment response. This characterises clinical heterogeneity that is revealed overtime. Four out of 15 HSTGs (26%) had manufacturer submissions that conducted a scenario analysis for treatment continuation rules, with subgroups related to health condition and age.
- Sources of patient heterogeneity and resulting recommendations
  - All HST submissions (15; 100%) were recommended, within their marketing authorizations, by NICE as an option for treating their respective diseases. Nine HSTGs (60%) received recommendations that were subgroup specific. After extracting what type of subgroups were recommended (either health or non-health related) we categorised these to review which sources of patient heterogeneity were acknowledged by NICE. This includes intervention-related factors, health conditions, biomarkers and age. Six HSTGs (40%) had recommendations with labels that were specific to both age and health conditions. Two HSTGs had recommendations that were specific to biomarkers and intervention-related factors respectively.

> NICE's ERG criticisms for the manufacturer's approach to address heterogeneity
- We also reviewed each respective ERG report. ERG criticisms are summarised in Table 2.

Table 2. NICE's Evidence Review Group (ERG) criticisms for the manufacturer's analytical approaches that address patient heterogeneity in economic evaluations

Manufacturer approach	ERG criticism	ERG recommendations
Individual patient simulation model was exploited as this best reflect the nature of disease (lipodystrophy)	Extrapolation of data inputs from another clinical study is inappropriate in the individual patient simulation model	Unclear whether the cost-effectiveness effects come from the whole patient population or that subgroup.
Multi-state model structure (to measure long term outcomes)	Multi-state model structure is overly complex due to limited transition rate data from rare disease cohort	A simpler state-transition or partitioned survival model to be used instead
Subgroups incorporated into cost-effectiveness estimates to determine if different subgroups impact the model's outputs.	Small sample size and post-hoc analysis leads to risk of selection bias	Adds uncertainty in the clinical effectiveness, treatment discontinuation and safety of the treatment at the licensed dose in clinical practice
Markov model estimated the acquisition costs during each cycle using both a Relative Dose Intensity (RDI) multiplier and the cumulative probability of not yet having discontinued treatment	Estimation the acquisition costs with both a RDI multiplier and cumulative probability results in double counting	RDI alone reflects the difference between the planned doses and doses received. Applying a cumulative probability on top of this will double count the cost-savings associated with treatment discontinuation.
Scenario analysis had an ICER that was sensitive to their assumptions on time to treatment discontinuation	Partitioned survival analysis to extrapolate time to treatment discontinuation under-estimates the proportion of responding cohort who remain on treatment	Log logistic survival curves allow for the declining rate of treatment discontinuation over time
Model assumptions included that there would be long-term benefits of post treatment discontinuation	Lack of evidence regarding the long-term benefits of post treatment discontinuation	Assumption about long-term benefits was removed from the model
Model assumed that no patient discontinued treatment in the base case	Assumption that no patient discontinues treatment is implausible	ERG conducted a scenario analysis where treatment is discontinued at a low rate (0.05% per year)

Conclusions

> Whilst patient heterogeneity is widely acknowledged across national pharmacoeconomic guidelines, there is a gap in explicit advice towards how to address heterogeneity analytically. A particular gap in the guidelines is how to appropriately incorporate patient heterogeneity in economic evaluations. Since 2013, there has been only one explicit and directive update in the NPG in Australia on how patient heterogeneity should be addressed.

> While the majority of HST submissions for very rare diseases were aligned with the NICE predefined scope in terms of heterogeneity of clinical benefits and subgroup analysis, inconsistent approaches in addressing heterogeneity issues in these submissions were identified. This could be due to a lack of specific guidance by NICE. Although the final NICE recommendations on these HSTs seemed not to have been impacted by patient heterogeneity, perhaps due to the fact they are ultra rare diseases, inconsistency in approaches indicate NICE reimbursement decisions for specific patient subgroups are neither systematic or transparent.

> Improving NPGs on addressing heterogeneity is increasingly important in optimal resource allocation under constraints, particularly for high cost rare diseases, and there is an urgent need for countries to address this.

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