Sub-group analysis in a recent NICE appraisal of the cost-effectiveness of endovascular stents

David Epstein
University of York
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  – Reasons for variation in model input data
  – Explained and unexplained variation

• How decision models might take account of explained variation in input data
  – Cost-effectiveness in subgroups
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• Example: Surgery for endovascular stents (EVAR)

• Conclusions
Introduction: Sources of variation in costs and outcomes

• Explained variation: heterogeneity
  – Attributable to clinical characteristics
  – Focus of this presentation

• Unexplained variation: sampling or parameter uncertainty
  – Random variation in data (i.e., unexplained)
  – (Probabilistic) sensitivity analysis
  – Not discussed further in this presentation
Example of explained vs unexplained variation

• Operative mortality after endovascular aneurysm repair (EVAR), from a registry
  – Mean = 190 / 8345 = 0.023
  – SD = 0.002 (represents total variation)

• But patients face different risks
  – Age, renal insufficiency, type of device …
  – Regression: decompose variation into explained and random factors
Evidence of sub-group effects

Figure 2. Survival of Patients Undergoing Endovascular Repair or Open Repair of Abdominal Aortic Aneurysms, Overall and According to Age.

Data are shown for all patients (Panel A), for those 67 to 74 years of age (Panel B), those 75 to 84 years of age (Panel C), and those 85 years of age or older (Panel D).

Odds ratio of operative mortality (30 days) was similar for all age groups (OR approx. 0.25). Source: Schermerhorn, 2008, *NEJM* 358: 2644-2645
Why is it important to take account of heterogeneity in input data?

1. Match values of model inputs to those of the eligible population (**generalisability**)
   - Variables in the model might be **correlated**, if both are influenced by the same clinical characteristic (e.g. age)
   - The model is more **transparent** and **consistent** if these relationships are made explicit (using regression)

2. Cost-effectiveness might differ by clinical characteristics (**prioritisation**)
   - May be efficient to limit approval only to most cost-effective subgroups

3. Estimate of average cost-effectiveness might need to take account that decision model is **non linear**
1. Correlation between model variables

Most models are populated with an estimate of the MEAN value for each input variable

Eg Operative mortality Mean 2.3%, SD 0.002
Disease specific mortality Mean 0.5%, SD 0.01
Other cause mortality, Life tables
Etc.
1. Correlation between model variables

Operative mortality and other cause mortality are not independent.

They are both to some extent influenced by age.

Characteristics/risk factors

Operative mortality and disease-specific mortality are not independent. They are both to some extent influenced by age.
1. Correlation between model variables

- Age
- Aneurysm size
- Other risk factors (renal, cardiac, pulmonary, etc)

Fitness index relative to age and aneurysm size

- Operative mortality
- Aneurysm cause mortality
- Other cause mortality
- Utility
- Complications
- Treat effects
- Costs

Model variables
## 1. Regression analysis (mean, se of coefficients)

<table>
<thead>
<tr>
<th></th>
<th>Operative mortality</th>
<th>Disease-specific mortality</th>
<th>Other cause mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age per year</td>
<td>0.07 (0.01)</td>
<td>0.04 (0.01)</td>
<td>0.043 (0.01)</td>
</tr>
<tr>
<td>Aneurysm diameter</td>
<td>0.30 (0.05)</td>
<td>1.32 (0.22)</td>
<td>0.56 (0.11)</td>
</tr>
<tr>
<td>Renal condition</td>
<td>0.68 (0.14)</td>
<td>N/S</td>
<td>0.33 (0.07)</td>
</tr>
<tr>
<td>ASA Etc…….</td>
<td>0.70 (0.17)</td>
<td>N/S</td>
<td>0.33 (0.07)</td>
</tr>
</tbody>
</table>
1. Matching input variables in model to expected values in eligible population

- The **eligible** population may differ from the study population, eg younger
- In principle, regression offers a **transparent** and **consistent** method of adjusting each input variable (operative mortality, HRQOL, costs etc) to match the clinical characteristics of the **treatment** population
2. Finding the most cost-effective subgroups

• Step 1.
  – Regression analysis to quantify effect of risk factors on model inputs (preferably micro data but also meta-regression)

• Step 2.
  – Define set of discrete subgroups of interest
  – If there are many risk factors (e.g. different comorbidities), then presentation of results may be complex and confusing
  – May need to create a “risk index”

• Step 3.
  – Predict model inputs for each sub-group
  – Identifying treatment effects in sub-groups may be difficult or require assumptions

• Step 4.
  – Run decision model for each sub-group
## 2. Results of EVAR decision model
By fitness index, age & aneurysm size

<table>
<thead>
<tr>
<th>Age</th>
<th>Good</th>
<th>Moderate</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>70</td>
<td>70</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>75</td>
<td>75</td>
<td>75</td>
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<tr>
<td>80</td>
<td>80</td>
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<tr>
<td>85</td>
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<td>85</td>
<td>85</td>
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</table>

- **EVAR is either more costly with no additional benefit,** or additional costs are greater than £30,000 per additional QALY.
- **EVAR costs £20-30k per QALY**
- **EVAR costs <£20,000 per additional QALY**
3. Estimate of average cost-effectiveness in the treatment population

- Conventionally, analysts set all model variables (costs, operative mortality, treatment effects etc) to a **representative value** (eg the mean) in the treatment population.
- However, models are usually **non-linear**
- Consequently even if a policy is cost-effective for this “representative person” this does not mean it is cost-effective on average for the population as a whole.
- Net losses in some segments of the population might outweigh net gains in other groups.
- Instead, we should calculate results (costs and QALYs) in each sub-group, and calculate a **weighted sum** according to the proportion of the treatment population in each cell.
### 3. Proportion of treatment population in each cell (EUROSTAR register)

<table>
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<tr>
<th>Age</th>
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<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>70</td>
<td>75</td>
<td>80</td>
</tr>
<tr>
<td>5.5 cm</td>
<td>13%</td>
<td>7%</td>
<td>3%</td>
</tr>
<tr>
<td>6.5 cm</td>
<td>4%</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>7.5 cm</td>
<td>2%</td>
<td>1%</td>
<td>1%</td>
</tr>
</tbody>
</table>
Advantages of subgroup analysis

• Part of growing interest in bringing together analysis of micro-data (e.g. by regression) and decision modelling
• Make decision model more transparent and consistent
• Adjust results of analysis (e.g. trial data) to match characteristics of eligible population (generalisability)
• Help target approval decisions to the most cost-effective sub-groups (prioritisation)
• (Possibly) more precise estimate of average cost-effectiveness where there is clinical heterogeneity and model is non-linear
Limitations of sub-group analysis

- Availability of data
  - Needs micro-data or possibly meta-regression
  - Treatment effects & interactions

- Other considerations
  - Usually requires a validated (and accepted) clinical risk-scoring instrument to be available
  - Some averaging of cost-effectiveness may be inevitable. Wide variation within groups.
  - Equity. May be unjust or unfeasible to limit use eg by age
  - Subjective criteria might be mis-reported by clinicians

- Subgroup analysis is most likely to be acceptable...
  - When clinicians already base decisions on a risk score
  - When there is evidence of interactions with treatment effect
END
Objectives: Cost-effectiveness

• **Outcomes**
  – Life time Quality-Adjusted Life Years (QALY)
  – Life time costs to the health service

• **Comparators**
  – Open repair
  – Endovascular stent (EVAR)

• **Patients**
  – Suitable for open surgery or EVAR, aneurysm >5.5cm
  – Results are stratified by
    • Age
    • Aneurysm size
    • Level of co-morbidity (or “risk of operative mortality”)
Method: Decision model
Structure

Conversion to open repair

Primary admission

No event

Death

Non fatal secondary re-admission

Equation 1: 30 day operative death

Equation 2: other cause death

Equation 3: Late AAA death

Equation 4
Parameters

• Baseline risks, after EVAR, depend on age, AAA size and comorbidities
  – Regression analysis using data from a large register (EUROSTAR with >8000 patients)
    • 30-day operative mortality – Logistic regression
    • Late aneurysm mortality – Exponential survival model
    • Late non-aneurysm mortality – Cox PH survival model

• Treatment effects, EVAR vs Open surgery
  – EVAR trial 1 / DREAM
    • Operative mortality Odds ratio=0.35
      – Assume constant Odds Ratio for all risk groups
    • Late aneurysm mortality: Hazard Ratio=2.5
    • Late non-aneurysm mortality: Hazard Ratio=1.07
Fitness index

- Many comorbidities are risk factors for operative mortality
  - Pulmonary function
  - Renal function
  - Cardiac disease, etc.
  - Risks are moderated by use of statins, anti-hypertensives etc
- This makes it difficult to present results as there are hundreds of possible combinations of characteristics and moderators
- No agreement among vascular surgeons on an objective risk scoring system, a subject of ongoing research and debate
- For this analysis, we simply use a relative fitness index with value between 1 - 4 where
  - 1 = good fitness, no comorbidities
  - 2 = moderate fitness, 2 x operative mortality of patient with same age and aneurysm size but no comorbidity
  - 4 = poor fitness, 4 x operative mortality of patient with no comorbidity
Conclusions of Schermerhorn:

• Average results similar to the RCTs (EVAR trial 1/DREAM)

• Operative mortality odds ratio (EVAR vs Open Repair) broadly constant for all age groups

• But absolute difference in operative mortality is greatest for oldest age group

• Survival curves converge in all age groups

• Greatest gain in life expectancy in oldest age group
Rates of mortality from non-aneurysm cause after EVAR and open repair

- Predicted non aneurysm mortality rate after open repair
- Predicted non aneurysm mortality rate after EVAR
- Hazard ratio for non aneurysm mortality after EVAR compared to open repair $H_{EVAR}^{\text{EVAR}}$
- Hazard ratio for non aneurysm mortality for patients after aneurysm repair compared with general population $H_{\text{LargeAneurysm}}$
- Non aneurysm mortality rate in the general population $\mu_0$
Costs

• Stent-graft ~ £5,000 per patient ex VAT
• Procedures including devices
  – Open: £9,900  EVAR £10,400
• Other costs
  – Re-interventions (EVAR trial 1)
  – Surveillance (after EVAR)
    • 2 CT in 1st year, 1 CT per year thereafter
Further details


• Forthcoming: NICE appraisal of endovascular stents