Sample size for non-inferiority CEA: a Fetal Fibronectin Screening case study

Andrew Briggs, Kathleen Boyd, John Norrie
University of Glasgow
Sarah Stock
University of Edinburgh
Overview

• Background to CEA
  – CE Plane, decision thresholds, net-benefits
• Threatened pre-term labour
• Can FFN screening help? a simplified model
• Non-inferiority design within a CEA
• Sample sizes
• Conclusions
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The cost-effectiveness plane

- New treatment more costly
- Maximum acceptable ICER
- New treatment more effective but more costly
- New treatment dominates
- New treatment less costly but less effective
- New treatment less costly
- New treatment less effective
- Existing treatment dominates
The cost-effectiveness plane and the ceiling ratio

- New treatment more costly
- Ceiling Ratio: $R_c$
- New treatment cost-ineffective
- New treatment more effective
- New treatment less effective
- New treatment less costly
The net-benefit statistic

The CE decision rule:

\[
\frac{\Delta C}{\Delta E} < R_C
\]

Rearranging:

**NB:** \[ R_C \Delta E - \Delta C > 0 \]

or

**NHB:** \[ \Delta E - \frac{\Delta C}{R_C} > 0 \]
The net-benefit statistic

Net-benefits on the cost scale:
\[ NB = R_C \Delta E - \Delta C \]

Variance and CIs for net-benefits:
\[ \text{var}(NB) = R_C^2 \text{var}(\Delta E) + \text{var}(\Delta C) - 2R_C \text{cov}(\Delta E, \Delta C) \]
\[ \left( NB - z_\alpha \sqrt{\text{var}(NB)} , \, NB + z_\alpha \sqrt{\text{var}(NB)} \right) \]
Power calculations for CEA using net-benefits

We know the mean and variance of the net-benefit statistic

\[ \hat{NB}_C = R_c \Delta \bar{E} - \Delta \bar{C} > 0 \]
\[ \text{var}(\hat{NB}_C) = R_c^2 \text{var}(\Delta \bar{E}) + \text{var}(\Delta \bar{C}) - 2R_c \text{cov}(\Delta \bar{E}, \Delta \bar{C}) \]

The problem at the design stage is to ensure adequate power to show significance

\[ (R_c \Delta \bar{E}^0 - \Delta \bar{C}^0) - z_\beta \sqrt{\sigma_{NB}^2} > z_{\alpha/2} \sqrt{\sigma_{NB}^2} \]

Substituting in standard expressions for mean, variance and covariance from sample data gives (after some messy manipulation)

\[ n > \frac{(z_{\alpha/2} + z_\beta)^2 \left[ R_c^2 (\sigma_{ET}^2 + \sigma_{EC}^2) + (\sigma_{CT}^2 + \sigma_{CC}^2) - 2R_c \rho \sqrt{(\sigma_{ET}^2 + \sigma_{EC}^2)(\sigma_{CT}^2 + \sigma_{CC}^2)} \right]}{(R_c \Delta \bar{E}^0 - \Delta \bar{C}^0)^2} \]
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Threatened pre-term labour

• Approximately 8% of women present with threatened pre-term labour during pregnancy
• Of those, approximately 20% will go on to deliver pre-term
• RDS is a complication of pre-term delivery with a prevalence of approximately 24%
• Of RDS babies, approximately 2.5% could die
Intervention and current management

• Administering steroids to the mother can result in a 54% reduction in RDS cases
• But woman has to be monitored in hospital
• Therefore, approximately 90% of women with threatened pre-term labour are admitted to hospital for prophylactic steroid administration and monitoring
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FFN screening

• Fetal Fibronectin tests are accurate for predicting pre-term labour
  – Approximately 80% sensitive and specific

• Offer the potential to provide a mechanism to screen those women with most to benefit from hospital admission and discharge rest
  – Less inconvenience to woman and her family
  – Lower costs for the health service

• Risks associated with false negatives
  – Increased morbidity (RDS)
  – Therefore increase mortality
Additional parameters to model cost-effectiveness

• Probability of admission to hospital following
  – ‘+’ve test assumed 100%
  – ‘-’ve test assumed 30%

• Cost of a hospitalisation for TPTL: £1,439

• Value of a statistical life: £1,000,000

• Value of morbidity (RDS) avoided:
  \[0.0257 \times £1,000,000 = £25,700\]
Simplified CE model

\[ \text{NMB} = \Delta H \cdot C_h - \Delta M \cdot R_c \]

Where:

- \( \Delta H \): Difference in proportion women hospitalised
- \( C_h \): Average cost of hospitalisation (£1,439)
- \( \Delta M \): Difference in proportion infants with severe morbidity (RDS)
- \( R_c \): Willingness to pay to avoid morbidity (£25,700)
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NI within CEA on the CE plane

$\Delta E$

$(NI \text{ margin})$

$2\%$

$(-0.06\%, -£526)$

£25,700/RDS avoided

$\Delta C$
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# Sample size table

<table>
<thead>
<tr>
<th>Power (%)</th>
<th>Sample Size</th>
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<tbody>
<tr>
<td>80</td>
<td>996</td>
</tr>
<tr>
<td>85</td>
<td>1139</td>
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<tr>
<td>90</td>
<td>1333</td>
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<table>
<thead>
<tr>
<th>Prop Hospitalised</th>
<th>Prop RDS</th>
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<tbody>
<tr>
<td>fFN Test</td>
<td>0.53436</td>
</tr>
<tr>
<td>No Test</td>
<td>0.90000</td>
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<tr>
<td>Difference</td>
<td>-0.36564</td>
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## Sample size table

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• Sample size for CEA rare in practice
• Ideal analyses would involve full economic modelling and appropriate design using value of information principles
• We had less time (and no funding)
• Lots of limitations we hope to explore
  – Making the model more sophisticated
  – Introducing parameter uncertainty
• Principle is that CEA can be used to set appropriate inferiority margins for NI designs