A value-of-information approach to sample size determination and decision-making in confirmatory clinical trials in small populations

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Levels of evidence requirements in rare diseases

Regulation (EC) 141/2000:

“patients with [rare] conditions deserve the same quality, safety and efficacy in medicinal products as other patients”

“orphan products should therefore be submitted to the normal evaluation process”

FDA Draft Guidance on Rare Diseases:

“The Orphan Drug Act […] does not create a statutory standard […] different from […] common conditions”
### Sample sizes for rare disease trials from clinicaltrials.gov database

<table>
<thead>
<tr>
<th>Sample size</th>
<th>Non-rare disease</th>
<th>Rare disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>500+</td>
<td>8%</td>
<td>1%</td>
</tr>
<tr>
<td>101 – 500</td>
<td>30%</td>
<td>13%</td>
</tr>
<tr>
<td>51 – 100</td>
<td>22%</td>
<td>19%</td>
</tr>
<tr>
<td>0 – 50</td>
<td>40%</td>
<td>67%</td>
</tr>
</tbody>
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Bell and Tudur Smith, 2014, *Orphanet J Rare Dis*, 9: 170
For rare diseases grouped by prevalence…

Hee et al. 2017, Orphanet J Rare Dis, 12: 44
Example of a trial in haemophilia A

E: tailored prophylaxis with recombinant factor VIII
C: usual care

Expected prob. of success on C, $p_C = 0.55$
Expected prob. of success on E, $p_E = 0.79$

Conventional sample size calculation:
- type I error rate, $\alpha = 0.05$ (two-sided)
- power, $1 - \beta = 0.9$
- total sample size, $n = 150$ (75 per arm)

Rare disease: size of total population to be treated = 4000

<table>
<thead>
<tr>
<th>600 on C</th>
<th>3250</th>
</tr>
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<tbody>
<tr>
<td>75 on C</td>
<td>75 on E</td>
</tr>
</tbody>
</table>

Trial cost: \$1,000,000 + \$5,000 per patient  
Additional cost for E: \$61,000 per patient  
Treatment success value: \$400,000 per patient

\[ E(\text{gain}) \text{ relative to all receiving C: if } p_C = p_E = 0.55 \]
\[ = -1,000,000 - 5,000 \times 150 - 61,000 \times 3250 \times 0.025 - 61,000 \times 75 \]
\[ = -11 \text{ million} \]
Rare disease: size of total population to be treated = 4000

| 600 on C | 75 on C | 75 on E | 3250 |

Trial cost: $1,000,000 + $5,000 per patient
Additional cost for E: $61,000 per patient
Treatment success value: $400,000 per patient

E(gain) relative to all receiving C: if $p_C = 0.55$, $p_E = 0.79$

\[-$1,000,000 \times 600 - $5,000 \times 150 \times 100 - $61,000 \times 3250 \times 0.9 + $400,000 \times 3250 \times 0.9 \times 0.24 + $400,000 \times 75 \times 0.24 = $103$ million\]
Impact of reducing to 80% power:

<table>
<thead>
<tr>
<th>448 on C</th>
<th>3440</th>
</tr>
</thead>
<tbody>
<tr>
<td>56 on C</td>
<td>56 on E</td>
</tr>
</tbody>
</table>

E(gain) relative to all receiving C: if $p_C = p_E = 0.55$

$-1,000,000 - 5,000 \times 112 - 61,000 \times 3440 \times 0.025$

$-61,000 \times 56$

E(gain) relative to all receiving C: if $p_C = 0.55, p_E = 0.79$

$-1,000,000 - 5,000 \times 112 - 61,000 \times 3440 \times 0.8$

$-61,000 \times 56 + 400,000 \times 3440 \times 0.8 \times 0.24$

$+400,000 \times 56 \times 0.24$
power = 0.8
power = 0.7
Expected Gain (\$/million) vs. pE

\[ \text{power} = 0.95 \]
power = 0.99
\( \alpha = 0.1 \)
$\alpha = 0.5$
Prior distribution
Design optimization: $E(gain)$ for optimal $\alpha$ for range of $n$

Optimal design has $n = 46$ (23 per arm)

$\alpha = 0.35$
\( \alpha = 0.35, \, n = 46 \)
Effect of population size – (i) on optimal trial sample size

Optimal sample size smaller for smaller population size $N$:

$$n \propto N^{1/2} \quad \text{for large } N$$

For small $N$ optimal to approve new treatment without a trial!
Effect of population size on optimal significance level

Optimal $\alpha$ larger for smaller population size:
- small $N$: $\alpha > 0.05$
- large $N$: $\alpha < 0.05$

Decision reflects population size
Summary

Trials in rare diseases do currently use smaller sample sizes

Value-of-information methods could formalise ad-hoc sample size choice, modify sample size according to population size by considering value of information gained, lead to clinical decision-making reflecting gain to population, do not increase information available from small trial.

Not the last word; but maybe part of a conversation.