Interim Sample Size Re-estimation: Safeguarding the Power of a Trial

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on behalf of the ALPHA Trial Group

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Introduction

- Rationale for re-estimating the sample size
- Process of conducting a sample size review
- Regulatory considerations
- Case study: Hand eczema trial (ALPHA)
- Summary
Rationale for sample size re-estimation

• Initial trial design stage:
  • Sample size assumptions based on information available
  • Uncertainty in assumptions
  • Potential for unpowered study

• Using data internal to the trial:
  • confirm or refute assumptions
  • Directly relevant patient population
  • Use same endpoint

• Check trial design is not unpowered
• Potentially revise sample size
Process for conducting a sample size review

- Nuisance parameters to be re-estimated
  - e.g. standard deviation, event rate, coefficient of variation, drop-out rate
  - using internal data at an interim analysis
    → adjust final sample size

- The sample size review should be conducted **blinded manner**:
  - Preserves the Type I error of the trial
  - Will not compromise the integrity of the trial
Regulatory considerations

**FDA**
- A blinded examination of the nuisance parameter can be made and compared to the assumption used in planning the study
- Can increase the sample size; not decrease the sample size
- Perform cautiously early in the study

**EMEA, CHMP**
- Where possible, use methods for blinded sample size reassessment that properly control the type 1 error
- Treatment effect should not depend on the interim results
- One sample size review preferable
ALPHA: ALitretinoin versus PUVA in HAnd Eczema

Design:
• Multi-centre, open, prospective, parallel group, adaptive RCT in patients with chronic severe hand eczema

Primary objective:
• To compare Alitretinoin and Psoralen combined with UltraViolet A (PUVA) as first line therapy in terms of disease activity at 12 weeks post planned start of treatment

Primary outcome Measure:
• Hand ECzema Severity Index (HECSI) at 12 weeks
ALPHA: Primary outcome measure

Hand ECzema Severity Index (HECSI)

- Very limited literature on HECSI available
  - Limited even further for our patient population

- Data tend to be very skewed (Hald 2009):

- Relative increase in score more clinically meaningful than an absolute increase
  - Absolute difference of 10 units is clinically more significant at the lower end of the HECSI compared to the upper end, for example
ALPHA: Minimum and maximum sample size

- Clinically relevant difference between treatment groups
  - Relative increase of 30% in treatment compared to the control group

- 80% power
- 2-sided 5% significance level
- 20% drop-out rate

- Need an estimate of the nuisance parameter,
  - i.e. coefficient of variation (CV) = s.d. / mean

**Minimum and maximum sample size**

<table>
<thead>
<tr>
<th></th>
<th>Minimum</th>
<th>Maximum</th>
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</thead>
<tbody>
<tr>
<td>CV</td>
<td>1.175</td>
<td>1.700</td>
</tr>
<tr>
<td></td>
<td>(s.d=33.9; mean=28.85)</td>
<td>(s.d=33.9; mean=20.3)</td>
</tr>
<tr>
<td></td>
<td>(Van Gils, 2011)</td>
<td>(Van Gils, 2011; Clinical opinion)</td>
</tr>
<tr>
<td>Number of patients</td>
<td>500</td>
<td>780</td>
</tr>
</tbody>
</table>
**ALPHA - Number of patients required for sample size review**

- Mean HECSI score, $\bar{Y}$ at 12 weeks is 28 (Hald 2009)
- Standard deviation, $\hat{\sigma}_Y$ is 33.9
- Above two assumptions lead to CV=1.2
- Estimate of the variance of the log transformed HECSI is given by (Koopmans, 1964):
  \[
  \hat{\sigma}^2 = \log \left( 1 + \frac{\hat{\sigma}_Y^2}{\bar{Y}^2} \right) = \log \left( 1 + \frac{33.9^2}{28^2} \right) = 0.9 = s^2
  \]
- Precision based approach (95% CI of the CV)

<table>
<thead>
<tr>
<th>Precision</th>
<th>Number of evaluable patients</th>
<th>Total number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>-0.093</td>
<td>+0.107</td>
<td>640</td>
</tr>
<tr>
<td>-0.109</td>
<td>+0.131</td>
<td>448</td>
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<tr>
<td><strong>-0.132</strong></td>
<td><strong>+0.168</strong></td>
<td><strong>291</strong></td>
</tr>
<tr>
<td>-0.167</td>
<td>+0.232</td>
<td>169</td>
</tr>
</tbody>
</table>
**ALPHA – Sample size re-estimation**

- Blinded sample size re-estimation
  - Aggregated estimate of the CV over both groups combined
    - Accurate estimate of within treatment group estimate of CV?
  - Pooled estimate of the CV within each treatment group (Wittes 1990; Birkett 1994)

- Determine conditional power of the trial
  - Conditioned on the variability at the interim analysis and treatment effect assumed at the design stage
  - Sample size required to give 80% conditional power

- Provide information to the Data Monitoring Committee
ALPHA – Re-estimated sample size

- Interim analysis:
  - revised estimate of the CV
  - sample size with conditional power of 80%

![Decision Tree Diagram]

- SS at interim analysis
  - New SS < 500
    - Final sample size = 500
  - 500 ≤ New SS ≤ 780
    - Final sample size = New SS
ALPHA: Safeguarding the power of a trial

- Funding Body requested to consider powering at 90%

- Response:
  - Require an increase to a maximum of 1040 patients
    - Not realistic in the UK
  - Sample size re-estimation: Safeguard the power of the trial at 80%
  - Study can still deliver a clear decision on treatment effectiveness
ALPHA – overview of considerations

- Requirement for sample size re-estimation considered at the trial planning stage
- A single re-evaluation of the sample size conducted
- Minimum sample size pre-specified
- Conducted blind to maintain overall type 1 error
- Timing considered to ensure sufficient level of precision in estimate of the CV

- Logistical considerations
  - plan for maximum sample size
    - Required number of centres to reach maximum sample size
    - Costings
    - Drug supply
**In summary**

- Sample size re-estimation recommended when uncertainty in the estimates of nuisance parameters
- Nuisance parameters re-estimated using data internal to the trial
- Should be conducted blind to treatment allocation to maintain Type 1 error and trial integrity

**Safeguards the power of a trial!**
References


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Questions?