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

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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

ALPHA
Comparing treatments for severe chronic 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

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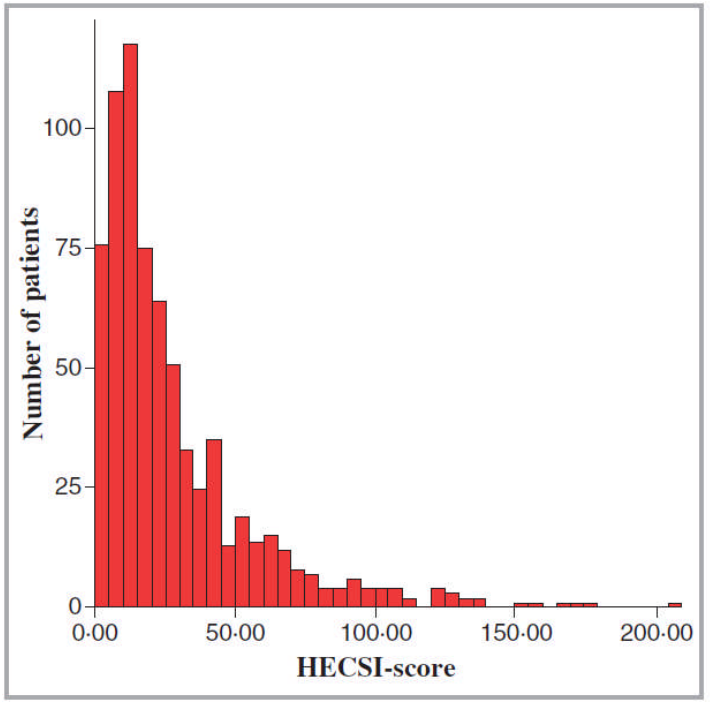
ALPHA: Primary outcome measure

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

	Minimum	Maximum
CV	1.175 (s.d=33.9; mean=28.85) (Van Gils, 2011)	1.700 (s.d=33.9; mean=20.3) (Van Gils, 2011; Clinical opinion)
Number of patients	500	780

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)

Precision		Number of evaluable patients	Total number of patients
-0.093	+0.107	640	800
-0.109	+0.131	448	560
-0.132	**+0.168**	**291**	**364**
-0.167	+0.232	169	212

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ALPHA –Sample size re-estimation

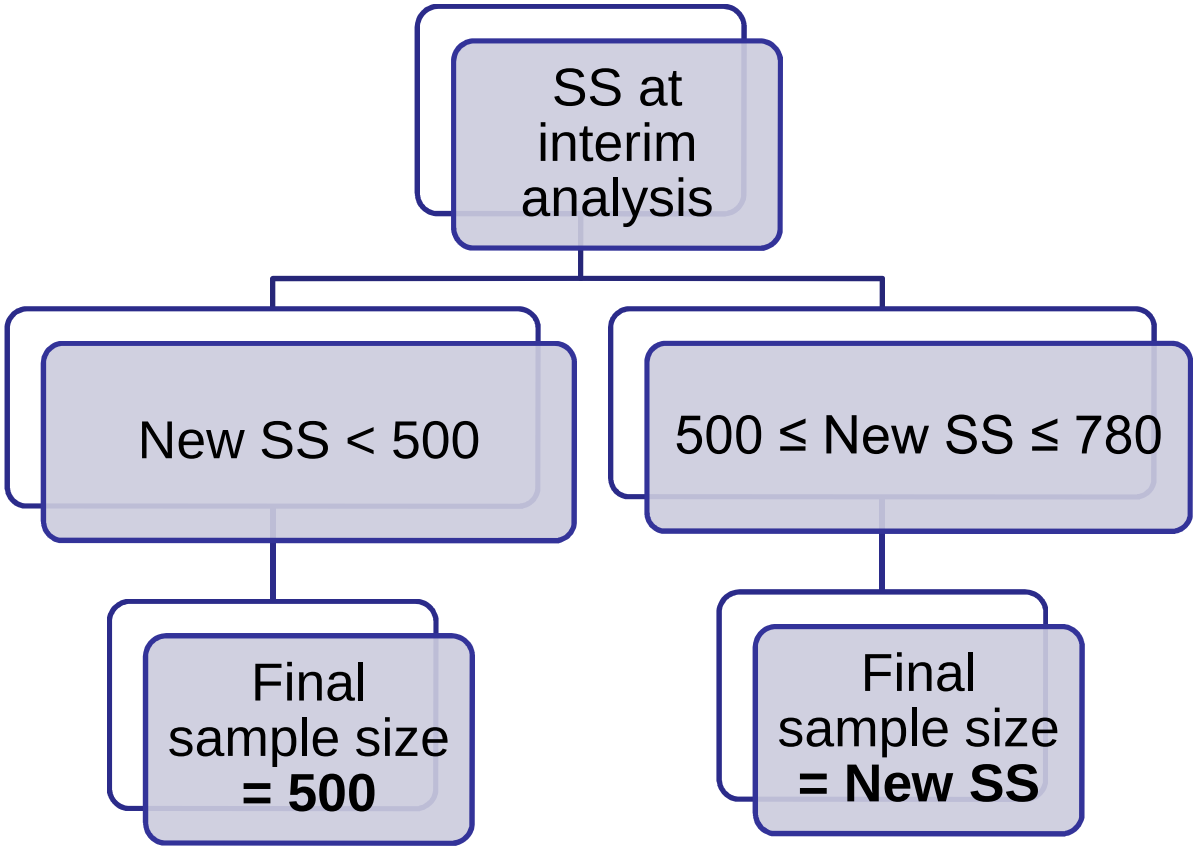
- Blinded sample size re-estimation
  - Aggregated estimate of the CV over both groups combined
    - Accurate estimate of within treatment group estimate of CV?
  - Pooled estimate of the CV within each treatment group (Wittes1990; Birkett 1994)

- 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%



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!

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Questions?

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