Session 10: The Design of Studies
Choosing a Methodology

10.1 Ordinal methods in general
10.2 Current status of ordinal methods
10.3 Issues with the proportional odds model
10.4 Issues with the sliding dichotomy
10.5 Simulation study
10.6 Proportional odds versus the sliding dichotomy
10.7 Conclusions / Discussion

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10.1 Ordinal Methods in General

- **Collapsing an ordinal scale to a binary scale will always discard potentially valuable information**
- **An ordinal analysis is likely to be efficient**
- **Even when key distributional assumptions are clearly violated an ordinal analysis should give greater insight**
- **Might need to make a difficult value judgement to assess whether the scale is truly ordinal (and consider the regulatory implications)**

10.2 Current Status of Ordinal Methods

- Ordinal methods have been used in a number of high profile published Phase III trials in stroke and head injury
- The drug regulatory authorities accept and even tend to encourage ordinal methods
- Grant reviewers and journal referees do not universally accept PO and/or SD as valid
- The characteristics of ordinal methods have been explored in detail in the OAST and IMPACT studies

10.3 Issues with the Proportional Odds Model

- **What if the proportional odds assumption is clearly violated?**
- **Will the same covariates necessarily be relevant for each cutpoint of the scale?**
- **Will the approach be credible to a clinical audience (especially if the goodness-of-fit test rejects the proportional odds assumption)?**

10.4 Issues with the Sliding Dichotomy

- Can the pooled trial data be used to develop (or refine) the predictive model?
- How many prognostic bands to use?
- How to define the bands?
- How to determine the point of dichotomy within each band?
- In general, for all the above, what degree of pre-specification is necessary?
- What if the odds ratios per band are heterogeneous?

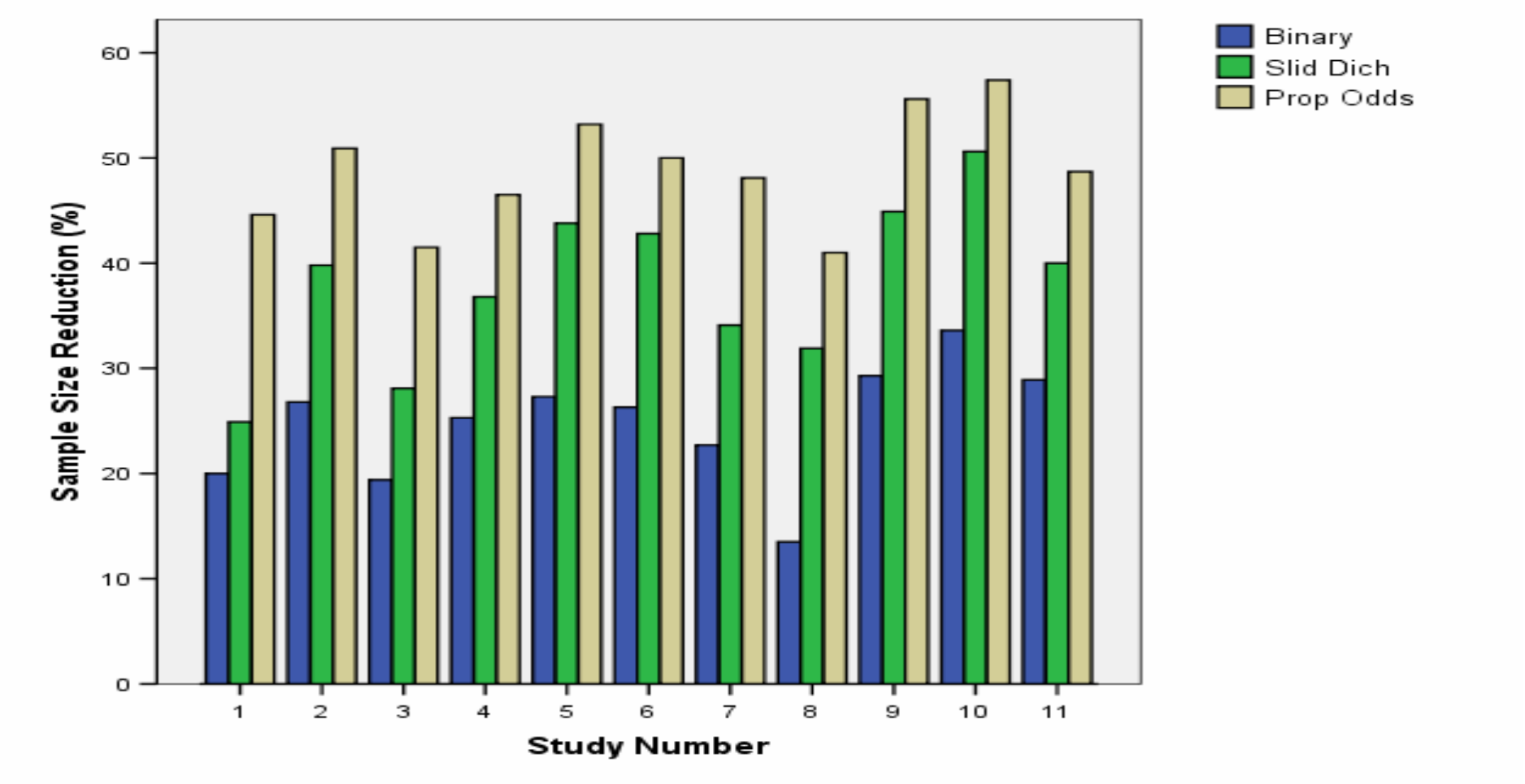
10.5 Simulation Study

- **2x400 patients sampled at random without replacement from each of 11 head injury studies**
- **Outcomes simulated for the 400 ‘placebo’ patients**
- **Outcomes with added treatment effect simulated for the 400 ‘intervention’ patients**
- **Treatment effect follows proportional odds model**
- **Analyse results using a range of techniques**
- **Repeat 1000 times, accumulate results, and derive sample size reduction relative to conventional dichotomous analysis**

Methods: Techniques Evaluated

- Conventional dichotomy, as reference
- Conventional dichotomy, with covariates
- Sliding dichotomy with covariates
- Proportional odds model with covariates

Sample Size Reductions Achieved



Conclusions from Simulations

- **Substantial benefits with covariate adjustment**
- **Ordinal analysis brings further substantial efficiency gains**
- **Proportional odds model betters sliding dichotomy (as deployed in this exercise)**

(See McHugh et al, Clinical Trials, 2010)

10.6 Sliding Dichotomy vs Proportional Odds

	Sliding Dichotomy	Proportional Odds
Statistical efficiency relative to conventional dichotomy	☺ ☺	☺ ☺ ☺
Reliance on powerful prognostic model	☹	☺
Reliance on distributional assumptions	☺	☹
Acceptability to Regulatory Authorities	☺	☺
Acceptability to clinicians (?)	☺	☹

10.7 Conclusions / Discussion

- **There is strong evidence that ordinal analysis can lead to substantial gains in trial efficiency**
- **The choice between the sliding dichotomy and the proportional odds model raises subtle issues, but the key point to take away is that either approach is preferable to the conventional dichotomous approach**
- **Head injury and stroke trials have historically been grossly under-powered**
- **So the efficiency gains demonstrated should be regarded as a partial solution to this problem and not an excuse to reduce trial sample sizes even further!**