Sample size

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Ethical: Protection of human subjects

- Nuremberg Code
  `http://ohsr.od.nih.gov/guidelines/nuremberg.html`
- Declaration of Helsinki `www.wma.net`
- ASA 1999, Ethical Guidelines for Statistical Practice
  `http://www.amstat.org/about/ethicalguidelines.cfm`
- ISI 2009, ISI Declaration on Professional Ethics
  `http://isi.cbs.nl/ethics0index.htm`

Good science

- Research methodology
- Pre-specification
- “compelling evidence”
- Consistent and robust results

ICH - Guidance documents

- ICH E1 Population Exposure: The Extent of Population Exposure to Assess Clinical Safety
- ICH E9 Statistical Principles for Clinical Trials
- Disease specific guidance

Legislation

- EU
  - Commission Directive 2005/28/EC, EU GCP Directive
  - Commision Directive 2001/20/EC, EU Clinical Trials Directive
- USA
  - Food and Drug Administration Amendments Act of 2007
- Rest of the world
  - Implemented in national law

More stakeholders are involved

More requirements from

- Health Technology Assessment (NICE, IQWiG, etc)
- Evidence Based Medicine
- Cochrane Centre

leads to requirement on transparancy and pre-specification

- registration of clinical trials
- publication of results
- CONSORT statement
- request for public access to protocols

Terminology

Sample size

- determination
- calculation
- justification

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- Discrepancies in sample size calculations and data analyses reported in randomised trials: comparison of publications with protocols
- Chan A, Hrobjartsson A, Jrgensen KJ, Gtzsche PC, Altman DG
- Objective: To evaluate how often sample size calculations and methods of statistical analysis are pre-specified or changed in randomised trials.
- Conclusion: When reported in publications, sample size calculations and statistical methods were often explicitly discrepant with the protocol or not pre-specified. Such amendments were rarely acknowledged in the trial publication. The reliability of trial reports cannot be assessed without having access to the full protocols.

BMJ 2008;337:a2299 http://dx.doi.org/10.1136/bmj.a2299

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- Reporting of sample size calculation in randomised controlled trials: review
- Charles P, Giraudeau B, Dechartres A, Baron G and Ravaud P
- Objectives To assess quality of reporting of sample size calculation, ascertain accuracy of calculations, and determine the relevance of assumptions made when calculating sample size in randomised controlled trials.
- Conclusions Sample size calculation is still inadequately reported, often erroneous, and based on assumptions that are frequently inaccurate. Such a situation raises questions about how sample size is calculated in randomised controlled trials.

BMJ 2009;338;b1732 http://dx.doi.org/10.1136/bmj.b1732

Altman, DG: Statistics and ethics in medical research. III How large a sample? BMJ 1980, pp 1336-1338, Vol 281.

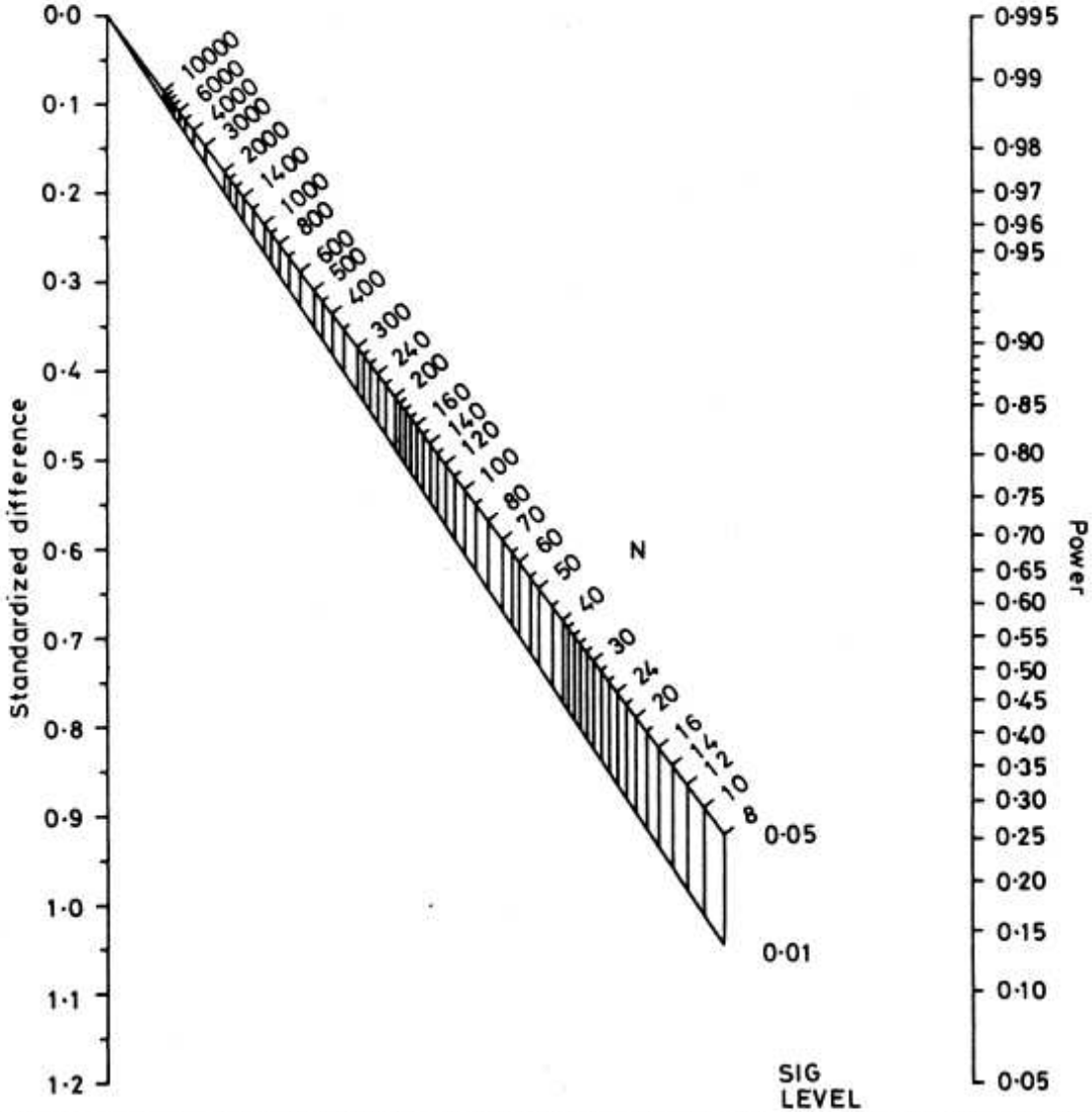

FIG 2—Nomogram for a two-sample comparison of a continuous variable, relating power, total study size, the standardised difference, and significance level.

Frequently meet issues 1/2

- Why adjust for dropout, thus powering the study for completer analysis; where completere analysis is not mentioned in ICH-E9
- Why adjust for dropout in a superiority study when the ITT analysis is the primary analysis
- Number of subjects may be given as a requirement - how should a sample size calculation for a single trial be made
- Often sample size is calculated for comparison of two treatments, but the final analysis is ANCOVA of, say, change from baseline with treatment and center with baseline value as covariate

Frequently meet issues 2/2

- More than one endpoint
- Multiplicity and test strategy - what is the alternative hypothesis
- Complex designs and stopping rules
- Sample size calculations are made in last moment
- Difficult to reproduce sample size calculations

Personal view

- Sample size determination is more than an item on a check list
- Sample size considerations are only a part of trial design and development program
- More effort should be used for providing rationale of assumptions (meta-analysis techniques)
- Challenges as more subgroup analyses are required
- As statisticians in the pharmaceutical/biotech industry we can and should be more involved in design and planning