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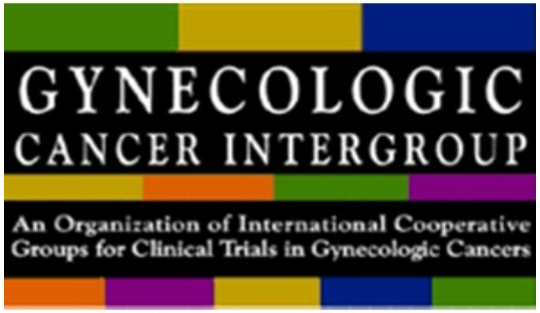

How To Design A Clinical Trial

Statistical Analysis

Andrew Embleton
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GCIG Education Symposium, November 2017, Vienna

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At what points do you need to consider statistics?

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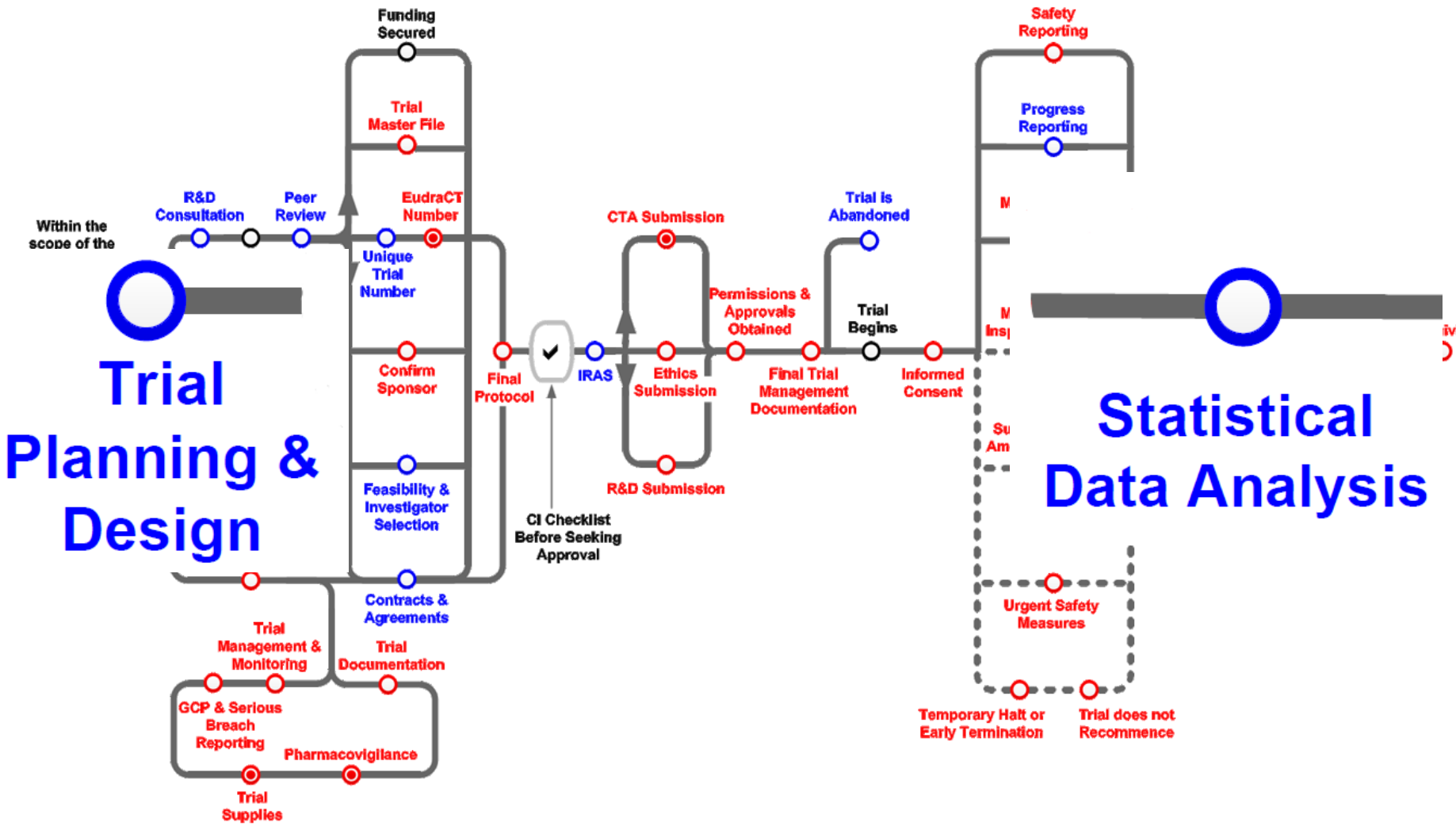

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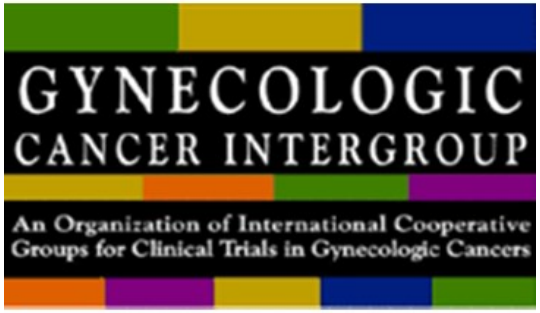
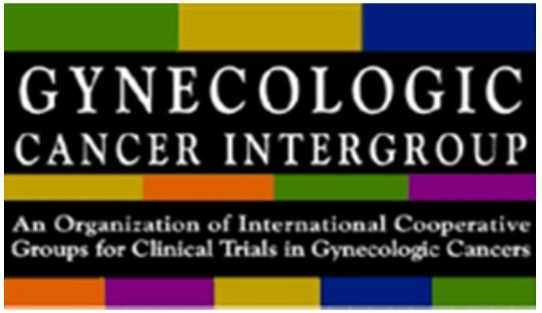


At what points do you need to consider statistics?

- Trial design
- Sample size calculations
- Statistical Analysis Plan

- Analysis



What question are we trying to answer?

- Before considering study design need to think carefully about the question we are trying to answer
- Getting the question right is essential to getting the design right
- We want to be able to answer the question we are interested in
  - If we use the wrong design we may not be able to answer our question
  - Even a good analysis can not save poor study design
  - In fact it is ethically wrong to conduct a clinical trial with the wrong design

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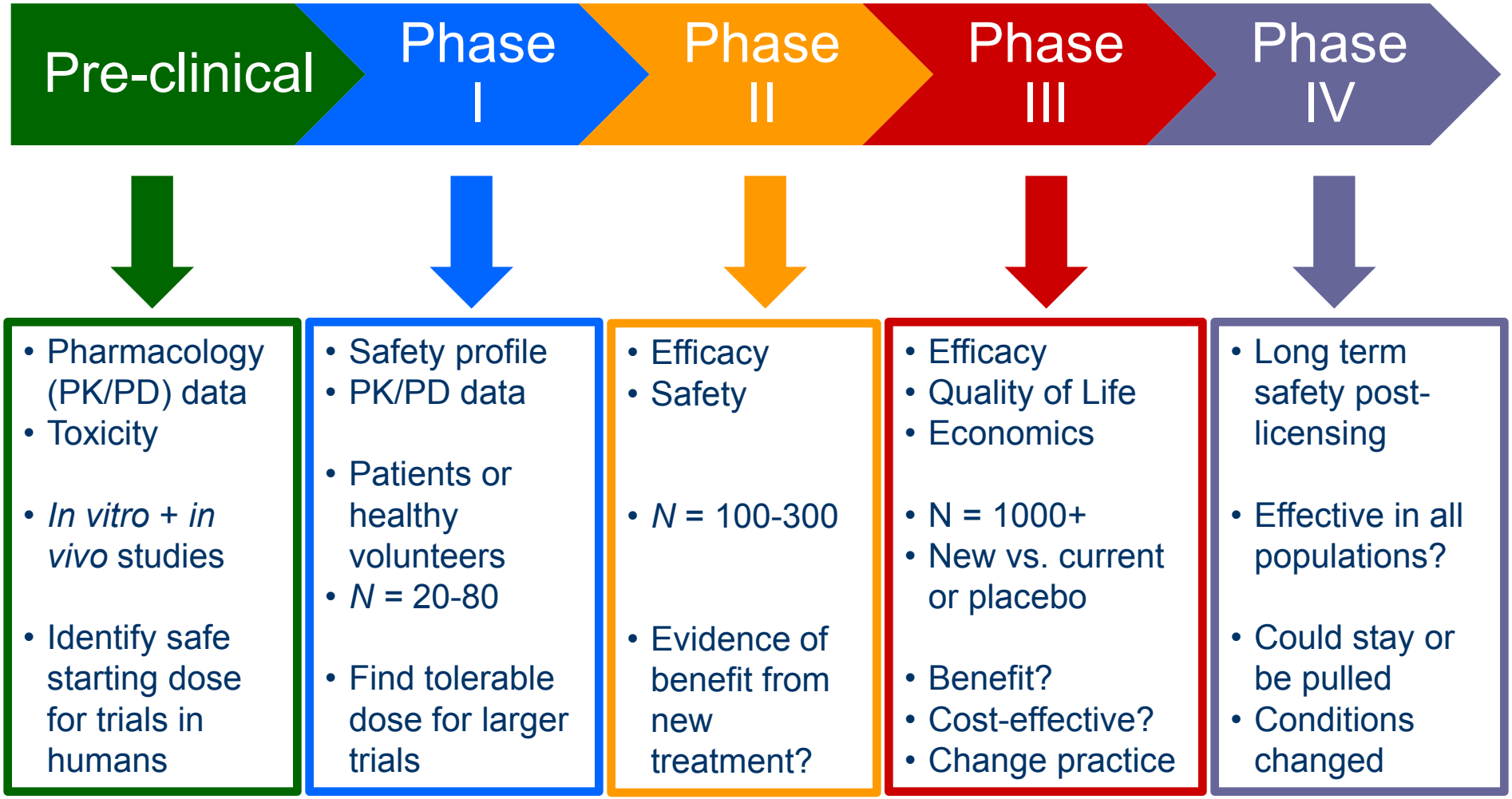
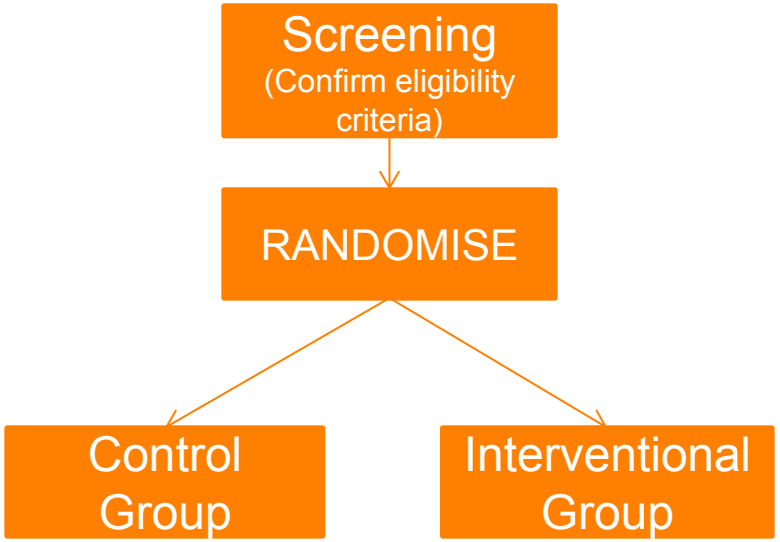
The phases of clinical trials



Parallel trial

- Standard A vs. B trial (or A vs. B vs. C vs…)
  - Two or more study groups evaluated prospectively
  - Each has one treatment regimen
- Straightforward

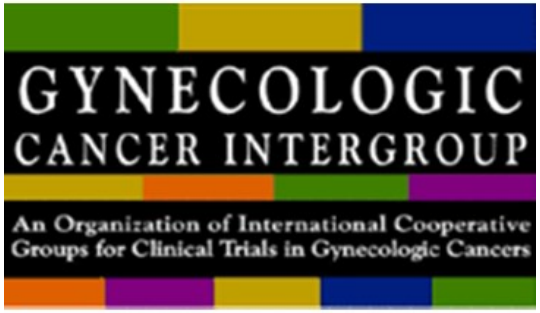


Trial design

- Crossover trials
- Factorial trials

- Cluster randomised trials
- n of 1 (type of crossover)
- Multi-Arm Multi-Stage (MAMS)

- Umbrella trials
- Basket trials



Superiority trials

- Superiority trials are the most common
- Used to demonstrate that one treatment is better than another treatment or a placebo (no treatment)

Non-inferiority trials

- Used to demonstrate that a treatment is no worse than an existing treatment
- Aim to show that effects are not worse by more than a pre-specified amount
- Our intervention may have other benefits over the competitor
  - e.g. cheaper, fewer side effects, easier to administer

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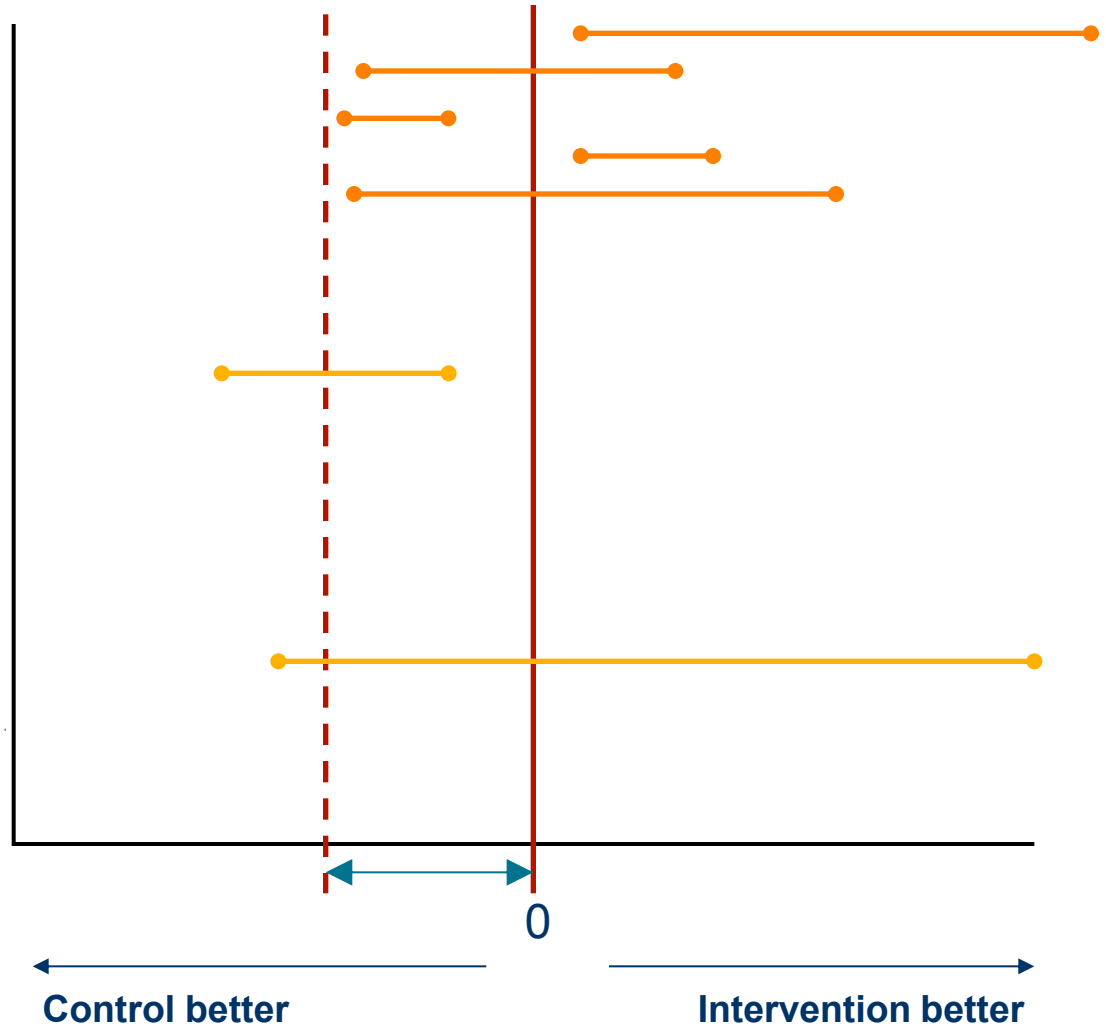
Non-inferiority trials

Noninferior

NOT noninferior
– CI goes below margin
– Intervention may be worse

NOT noninferior
– CI goes below margin
– Intervention may be worse



CI

acceptable margin

Trial design

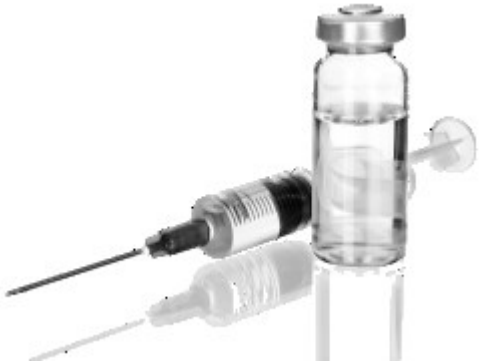
- Good design is one of the most important aspects of a clinical trial
  - design trumps analysis: complex analysis may improve a study but never fully compensates for poor design

- Poor design:
  - could cause a useless treatment to be used in patient care, wasting resources or a promising treatment to be wrongly abandoned
  - is unethical to participants
  - wastes valuable resources

Sample size calculations

- Too few patients:
  - Important treatment effects may be missed
  - May show a treatment works when it doesn't
- Too many patients:
  - Unethical to put more patients at risk
  - Spend extra time and money
  - May delay important results from the trial
  - Delay future trials

Sample size calculations

		Our decision	
		Fail to reject H_0 (negative result)	Reject H_0 (positive result)
Reality	H_0 correct	*Wondermab* is not effective	Recommend *Wondermab*, but doesn't actually work
	H_1 correct	Conclude *Wondermab* doesn't work, when in fact it does	*Wondermab* is effective

Sample size calculations

		Our decision	
		Fail to reject H_0 (negative result)	Reject H_0 (positive result)
Reality	H_0 correct	Correct!	Type I error (false positive)
	H_1 correct	Type II error (false negative)	Correct!

Sample size calculations

- **Significance:** Probability that we reject the null hypothesis (H_0) given that the null hypothesis (H_0) is true (top right box)
  - e.g. The probability of detecting a significant difference when the treatments are really equally effective

- **Power:** Probability that we reject the null hypothesis (H_0) given that the alternative hypothesis (H_1) is true (bottom right box)
  - e.g. The probability of detecting a significant difference when there really is a difference

Sample size calculations

- **Significance**
  - probability of type I error = probability of concluding a difference when there is none
  - α (alpha)
  - Often 5% (0.05)
  - Linked to p-values

- **Power**
  - 1 – probability of type II error = probability of detecting a difference when one exists
  - 1 – β (beta)
  - Often 80% or 90% (0.8 or 0.9)

High power and low significance…

- Can't have both with the same sample size

- Decrease significance → decrease power
- Increase power → increase significance

- No "best" balance

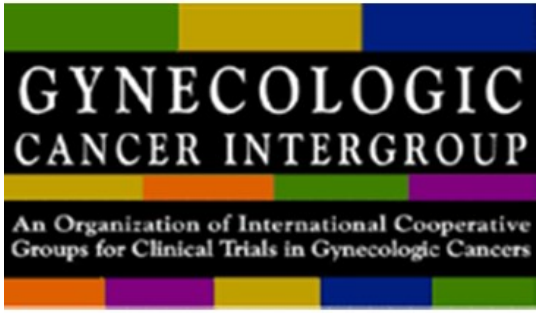
Four factors involved in calculation

- Significance level
  - As this increases the sample size will decrease
- Power
  - As this increases the sample size will increase
- Effect size
  - As this increases the sample size will decrease
- Variability
  - As this increases the sample size will increase

In reality…

- ...the choice of sample size is a compromise between:
  - the budget
  - how many patients are likely to be available
  - credibility

- Sample size calculations should be used as a guide to how many patients might be required to answer our question



Statistical Analysis Plan (SAP)

- The protocol provides a wide range of information on the trial including the background, objectives, design, methodology, statistical considerations, and organisation
- SAP contains more detail on the statistical aspects of the trial design and analysis
- Primarily the trial statistician, with input from other members of the trial team
- Written and finalised prior to database lock and unblinding of data (or prior to being given access to data in the case of unblinded trial)

Prespecification

- Reduce opportunities for bias
- Anticipate problems in advance
- Quick turn around of results once database locked

- Although there are opportunity to make changes with protocol and SAP amendments during the trial:
  - sample size recalculation, adaptive trial design

Prespecification

ICH E9:

"For each clinical trial…all important details of its design and conduct and the principal features of its proposed statistical analysis should be clearly specified in a protocol written before the trial begins. The extent to which the procedures in the protocol are followed and the primary analysis is planned a priori will contribute to the degree of confidence in the final results and conclusions of the trial"

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Contents

- Design
- Outcome measures
- Sample size calculations
- Data collection
- Statistical analysis
- Dissemination of results

Analysis

- recruitment: number screened, enrolled, randomised
- baseline characteristics (which, categorisation)
- description of follow up (number of person years)
- treatment details
- endpoints: definitions, analysis methods
- subgroup analyses
- safety analyses

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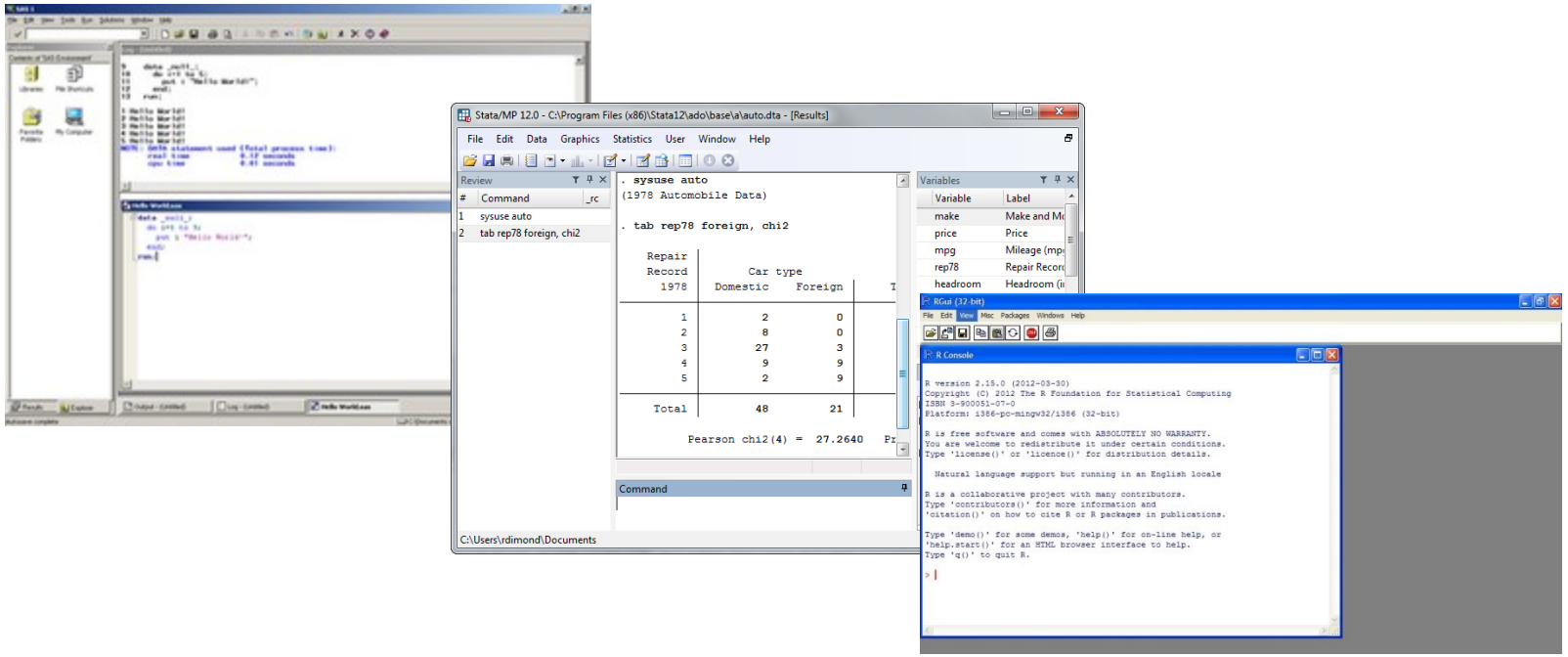
Software

- SAS/Stata/R



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Trial reporting guidelines

- CONSORT elaborates on the following areas:
  - Treatment allocation – what is so special about randomisation
  - Randomisation and minimisation
  - Steps in a typical randomisation process
  - Blinding terminology
  - Early stopping
  - Intention-to-treat analysis

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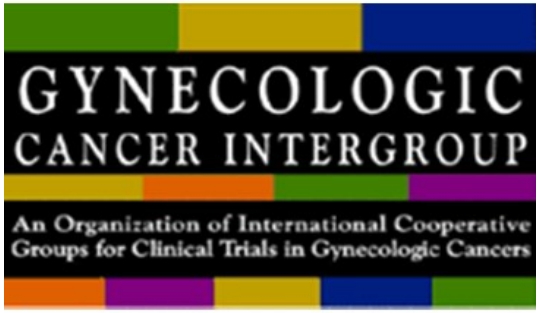

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