

## **Submitting a preliminary application**

# **The Importance of Methodological Input to Clinical Trial Protocols**

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Board**

## Trial design

- ▶ The EME programme is broadly aimed at supporting 'science driven' studies with an expectation of substantial health gain. The clinical studies are likely to be mostly randomised controlled trials (RCTs) but other forms of evaluation appropriate for the intervention under study will also be supported. This resource is primarily aimed at supporting trial design.
- ▶ The EME programme is very happy to receive applications that include pilot or feasibility work as part of a proposal for a wider study. We will also consider proposals for a stand-alone pilot or feasibility study, however there would be an expectation that such work could lead to a later full study as part of the EME programme.
- ▶ The EME programme is also keen to fund trials with adaptive designs.
- ▶ Adaptive trial design refers to a clinical trial methodology that allows trial design modifications to be made after patients have been enrolled in a study, without compromising the scientific method. In order to maintain the integrity of the trial, these modifications should be clearly defined in the protocol.
- ▶ Examples of adaptive trial designs include dropping a treatment arm, modifying the sample size, balancing treatment assignments using adaptive randomisation or simply stopping a study early for success or failure.

## Completed early clinical studies, established proof of concept in man – where next?

- ▶ Is a larger, efficacy trial needed now?
- ▶ Can you convince the EME Board (the Board) that your clinical question really needs an answer?
- ▶ **Do not take anything for granted – the Board will need to be convinced not only about the question, but also about how you are intending to answer it.**

## Methodological Input

- ▶ Methodology only becomes relevant once you have convinced the Board that the research needs to be done.
- ▶ However, competent and professional methodology can make the difference between a poor or mediocre application and an excellent one with a competitive edge.
- ▶ You should consider the following questions:
  - ▶ Who are your **methodological collaborators**?
  - ▶ Are you linked to a **recognised clinical trials unit**?
  - ▶ Who is the **trial statistician**?
- ▶ It is very important to give this much consideration – and make sure your methodological collaborators check, but preferably **write**, the relevant parts of the application.
- ▶ Your commitment to methodological rigour is much more convincing if the methodologists are **co-applicants** rather than just named consultants.

## The Preliminary Application Form

- ▶ There are two key places in the application form that can show the Board that you have fully considered the methodology and the involvement of methodologists.
  - ▶ Section D – Project Summary
  - ▶ Section H – Team Expertise, in particular H1, asks for an account of the team assembled and the skills and expertise each member will provide
  
- ▶ Here we focus specifically on three methodological issues which will need to be fully addressed in the application form:
  - ▶ Overall design, including allocation to intervention groups
  - ▶ Sample size calculations & recruitment
  - ▶ Data analysis

## Overall Trial Design

- ▶ Pay careful attention to the nature of the control group(s).
- ▶ Randomisation is virtually essential – you are likely to have a hard time convincing the Board to accept a quasi-experimental design or observational study unless you have convincingly shown that there is no alternative.
- ▶ Do you intend to randomise individuals or groups (clusters)? Is the unit of study the patient or person/service providing the care? Blinding or masking is very important – try to include wherever possible.

**Try to keep design as simple as possible.**

**This will make life easier and facilitate recruitment, if nothing else.**

- ▶ The planned interventions
  - ▶ Are these to be delivered to individual patients or to groups of patients?
- ▶ Allocation to treatment groups
  - ▶ Use a remote randomisation service – telephone or web-based - preferably provided by an established trials unit.
  - ▶ Secondary options can include ready-prepared lists of random numbers or boxes of sealed envelopes.
  - ▶ Describe *precisely* how it will be done.

## Randomisation

An example: “Following written informed consent, participants will be individually randomised via a telephone service provided by the Utopia Clinical Trials Unit. After first stratifying by treatment centre and sex, the randomisation procedure will involve the use of randomised permuted blocks with a randomly-chosen block size of either 4, 6 or 8.”

- ▶ Do not attempt to stratify by a large number of factors.
- ▶ Stratify by recruitment centre and possibly one or two key prognostic factors only.
- ▶ The analysis can be designed to cope with other prognostic data, as long as it is collected prior to randomisation.
- ▶ You might wish to consider some form of minimisation algorithm (with a stochastic or random component).

# Elements of a Sample Size Calculation

The following applies to a trial aiming to demonstrate efficacy, assumed to be the goal of most EME trials (sample size calculations for equivalence or non-inferiority designs require a more subtle approach).

- ▶ Specify the primary outcome measure.
- ▶ Specify the null hypothesis, and any subsidiary assumptions (estimated recovery rates in the control group, for example).
- ▶ Specify the size of the intervention effect you expect to detect (i.e. the alternative hypothesis).
- ▶ Specify the significance test to be used (t-test, ANOVA, chi-square, etc.).
- ▶ Specify the significance level (one- or two-sided?)
  - typically 0.05.
- ▶ Specify the required statistical power
  - typically 80%.
- ▶ Calculate the required sample size.
  
- ▶ **Check the sensitivity of your results to changes in the assumptions you are prepared to make (estimated recovery rates in the control group, for example).**

# Sample Size Calculation

## - specifying the Effect Size

- ▶ Effect size – you need to be able to define a *threshold of clinical significance*. Effects smaller than this are of no clinical interest; larger effects should not be missed. This threshold might vary with different stakeholders.
- ▶ This is the most difficult part! It is *not* the province of the statistician. Do not use your pilot/platform data as the sole justification for your calculations. Estimates from pilots are by their nature imprecise and likely to be a bit optimistic. Look for and use other sources of information.
- ▶ This is frequently one of the least credible components of a trial application. All the numbers you use in your sample size calculations must be explicitly justified in terms of the context of your own trial.

## A Hypothetical Example of a Poor Sample Size Calculation

“Our pilot investigation showed that the relapse rate in the control group was 50% and that in the intervention group it was 25%.

A Pearson chi-square test with a two-sided significance level of 0.05 would have 80% power to detect a difference between 50% and 25% if the trial contained 66 participants in each of the two groups.”

## A Hypothetical Example of a more convincing Sample Size Calculation

“Our pilot investigation showed that the relapse rate in the control group was 50% and that in the intervention group it was reduced to 25%. Previous studies (refs) indicate that relapse rates in the control condition are likely to be between 35% and 65%. We have consulted 20 clinicians, 10 service users and 10 informal carers, and the consensus view is that an absolute drop in relapse rates of at least 10% would be of clinical importance. Anything less would have little significance for the patients or their carers.

Using a variety of plausible values for the control group relapse rate, a Pearson chi-square test with a two-sided significance level of 0.05 would have 80% power to detect an absolute drop in relapse rates of 10% (from 50% to 40%, for example) if the trial contained about 400 participants in each of the two groups.”

- ▶ Therefore it is important that the sample size is correct for the question being addressed as an underpowered trial is likely to lack credibility.

## Final Sample Size Considerations

- ▶ You need to consider how sensitive your estimated sample sizes are to the assumptions concerning control group event rates/outcomes and the size of the effect you are looking for. Do not look for spurious precision.
- ▶ **Your assumptions concerning effect sizes need to be explicitly justified and to be credible (and not solely based on imprecise pilot data).**
- ▶ It is not usually necessary to consider allowances for stratification or covariates in the sample size calculations— by simply adopting a conservative approach one hopes that the allowance for these in the analyses will actually improve power.
- ▶ Power is traditionally set to be 80% but increasingly investigators are using higher values (e.g. 90 %).
- ▶ Significance levels should usually be set at 0.05 but make sure you consider whether you need to adjust to allow for multiple testing (if your test affects multiple outcomes you will often be expected to adjust the individual significance levels to ensure that the overall significance level remains at the nominal value, 0.05). Sample size calc. should also taken into account possible drop out, non-compliance etc
- ▶ Have you made allowance for cluster randomisation? Have you made allowance for patients receiving their therapy in groups? These often require *substantial increases* in sample size. In the case of group therapies it may also suggest changes in allocation ratios

## Recruitment

- ▶ Large samples (and ability to generalise) generally require multi-centre designs.
- ▶ Multi-centre trials should be facilitated by links to and support from a disease specific clinical research network (<http://www.ukcrn.org.uk/index/networks.html>) where possible
- ▶ Both randomisation and analysis of the subsequent results should generally involve stratification by recruitment centre.
- ▶ Recruitment needs to take into account participant drop out rates.
- ▶ You need to be able to convince the Board that you will be able to recruit the required number of participants to the trial. Too much optimism concerning recruitment rates is a major contributor to a failing trial.

*Lasagna's Law which states "In clinical research the prevalence of any disease falls to about 10% of what you thought it was the day you start to look for cases for your study"*

## Sample Size, again

The Barriers to Progress – comments received in progress reports:

- ▶ *“Recruitment has been slower than anticipated....”*
- ▶ *“Slow recruitment of patients...”*
- ▶ *“Recruitment has been slower than expected”*
- ▶ *“... delay in identifying suitable subjects for recruitment...”*
- ▶ *“Recruitment has been hard work”*
- ▶ *“Recruitment of GPs and patients was initially very slow indeed”*
- ▶ *“The second centre ... got off to a slow start ... The second centre ... had not recruited any subjects...”*
- ▶ *“....slow recruitment in the .. centre...”*

**Do *not* be tempted to propose over-optimistic effect sizes and correspondingly inadequate sample sizes to alleviate potential recruitment problems!**

## Details of Planned Analysis

- ▶ Ask the trial statistician to describe these\*.
- ▶ The Board would expect the method of analysis to be fully consistent with the design of the trial. In particular, it should allow for any stratification used in the randomisation procedure.
- ▶ Covariates should be specified in advance of seeing the data.
- ▶ EME studies may provide an opportunity to undertake a health economic evaluation. If health care evaluations are being considered these should be taken seriously – involve an economist. Ideally, the analysis of clinical and economic outcomes should be consistent.

\*They are not needed in great detail – but enough for the statisticians on the Board to be confident that there has been appropriate methodological input. If your application is successful, and once the trial has started the Trial Steering Committee is likely to ask the trial's statistician for a detailed trial analysis protocol.

# Adding Mechanisms Evaluation

- ▶ So far, we have restricted the discussion to methodological aspects of **Efficacy** evaluation. On the whole, the methods are well-established and the problem is mostly one of ensuring good practice.
- ▶ What about **Mechanisms**?
- ▶ Competent methodological (particularly statistical) input to mechanisms evaluation is even more essential.
- ▶ Much of the statistical work on evaluation of biomarkers as prognostic indicators (as in stratified medicine), treatment-effect mediators (potential surrogate outcomes), for example, is in its infancy.
- ▶ Beware of **confounders** (particularly those that are not measured).

- ▶ **Blinding:** A procedure in which one or more parties to the trial are kept unaware of the treatment assignment. Single-blinding usually refers to the subjects being unaware, and double-blinding usually refers to the subjects and investigators. Sometimes blinding is referred to as masking.
- ▶ **Block Size:** In a multicentre study subjects are randomly allocated to their study medication. Treatments are randomly organised in blocks so that an equal number of patients in each block will receive each of the treatments. The size of the block depends on the number of patients that each site is expected to recruit along with the number of treatment groups. For example, a 2 treatment group study with a block size of 4 could have blocks: AABB, ABAB, BABA, BBAA etc. Putting these together would give a randomisation schedule AABBBABBBABA...And therefore after every multiple of 4 subjects there will be an equal number of subjects allocated to treatment A and treatment B. Randomisation schemes are made of randomly allocated blocks.
- ▶ **Clinical Significance:** Any change in the patient's clinical condition (which may or may not be due to treatment) which is regarded as being important. Sometimes changes observed in clinical studies may prove to be statistically significant but they may not be clinically significant (eg. changes in particular blood tests).
- ▶ **Minimisation:** A method of randomisation where the treatment allocation for each subject is centrally controlled in an attempt to balance the split of treatment allocation across numerous strata. This is an example of dynamic allocation that minimises the imbalance of patients in treatment groups and strata while still maintaining an element of chance in the allocation.
- ▶ **Randomisation:** The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias. Randomisation schedules are often made of blocks (see block) and can be stratified (see stratified) or can be performed using dynamic methods like minimisation (see minimisation).
- ▶ **Stratification:** A method of randomisation where each strata (eg each centre, or each gender within centre) has an individual randomisation scheme in an attempt to ensure a balance of subjects allocated to each treatment group in a trial.

## Useful References

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# Further References

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