Good Study Design and Analysis Plans as Features of Ethical Clinical Research

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Outline

- The role of an IRB statistical reviewer
- The connection between good study design and statistical methodology and ethical clinical research
- Three categories of research methodology
- Examples
- Recommendations

The Role of an IRB Statistical Reviewer

- Serve as a resource to non-statisticians (IRB members, investigators)
- Review protocols submitted to the IRB
- Focus on three categories of research methodology:
  - Study Design
  - Data Analysis/Statistical Methods
  - Sample Size Considerations

Don’t most protocols already have statistical input/review?

- Some protocols have not had any (or very little) statistical input/review
- Others have received inadequate input/review
- Some protocols are well designed from a statistical point of view, but are not designed with an emphasis on *ethical research in humans*

The Connection to Ethical Research in Humans

- Need to balance the risk to subjects against potential benefit to science and society
- The subject should have the right to avoid risks that have little chance of benefiting science or society
- Impossible to do a complete risk/benefit analysis without a review of the study design and analysis plans

The "Take Home" Message

- A poorly designed or incorrectly analyzed study cannot benefit (and in fact, may be detrimental) to science and society in general

- A beneficial new treatment may be deemed ineffective or vice-versa

The “Take Home” Message (continued…)

- A study may inappropriately result in changes in patient care or recommendations for public health

No risk to study subjects in this setting is justifiable!

Three Categories of Research Methodology

1. Study Design
   - *General study design*
   - *Outcome definition*
   - *Bias*
   - *Controls*
   - *Blinding*
   - *Randomization*
   - *Interim monitoring/analysis*

2. Data Analysis/Statistical Methods

   Do we know how the data will be analyzed and are those methods appropriate?

3. Sample Size

   Is there an adequate justification of the sample size? (Not necessarily based on power considerations)

Study Design Example

Lack of blinding in a clinical trial

- Clinical trial of a new medication of an unusual color versus placebo
- Treating clinicians are aware of the treatment assignment (the study is not blinded)
- Clinicians may also administer concomitant medication if deemed necessary

- The decision to use concomitant medication could be influenced by the clinicians' knowledge of the treatment group
- This may lead to bias with an under- or over- estimation of the treatment effect
- Subjects may have been exposed to risk unnecessarily since the study question may not be answered

Data Analysis/Statistical Methods Example

Lack of consideration for the impact of side effects

- In a placebo controlled trial, side effects may cause sicker subjects to drop out of the drug arm, leaving only the healthier subjects
- A comparison of “study completers” will be biased in favor of the drug arm
- The study question will not be correctly addressed

Data Analysis/Statistical Methods Example 2

Failure to account for correlated outcomes

- Consider a clinical trial for a new versus standard treatment of a skin condition
- Different sites on the body are randomized to the two different treatments
- Outcomes are pain and patient satisfaction

Failure to account for correlated outcomes

- Proposed analyses comparing treatments assume that all outcomes are independent
- This analytic error may result in a lack of a significant difference between treatments where one exists
- Ignoring the correlation between outcomes on the same individual leads to a loss of power

Sample Size Issues

Scientific perspective: there should be enough subjects to address the study question and to ensure that the correct conclusion has been reached

Sample size is often, but not always, based on statistical power *(the ability to detect an effect or an association if one truly exists)*

Ethical perspective:

1. If there are too *few* subjects, the investigator cannot adequately address the study question
   - A “null” result may either be due to a true lack of effect or due to a lack of power
   - The study question will not be addressed and no risk (or time effort) to the subject is justifiable

2. If there are too *many* subjects enrolled than are needed to address the study question, then too many subjects have been unnecessarily exposed to risk

In general,

no more patients than are needed to answer the study question should be enrolled

Sample Size Example

Basing the calculation of sample size on the wrong outcome measure

- Consider a clinical trial for a new mobility device
- The primary outcome was the percentage of successful transfers from a bed to a wheelchair during a fixed time period (a continuous outcome ranging from 0 to 100%)

- Sample size calculations were based on whether or not a successful transfer occurred during that time period (a dichotomous “yes/no” outcome)
- Requested sample size was not appropriate for the study
- In this case, it’s likely that the study could be conducted with *less* subjects than requested
- More subjects may have been exposed to risk than necessary

Recommendations

- Consult a statistician whenever initiating a study (my highly biased opinion…)
- Investigators learning methods of human research should specifically examine the ethical implications of a poorly designed study
- IRBs should have a biostatistical reviewer as an advisor (good) or member (better)

Reference:

Weinberg JM, Kleinman KP. *Good study design and analysis plans as features of ethical research with humans*. IRB. 2003 Sep-Oct; 25(5):11-4.