On reading the literature of clinical trials

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Reading the literature of clinical trials

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Reading the literature of clinical trials

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How to succeed in clinical trials

- **Use surrogate outcome to reduce sample size and impress cost conscious funding agency**
- **Data dredge until you find a "significant" result**
- **Use a composite outcome when none of the outcomes alone yield "significant" results**
- **Consider only "evaluable" patients in analyses**
- **Discard certain events in analyses**
- **Perform analyses by treatment received**
- **Test a new (and preferably high tech) treatment and show it to be superior to current standard**
- **Reach a conclusion people want to hear**
- **Do a lot of small scale short term trials and publish only those that yield positive results**
- **Do only trials in which you are 1st (if not sole) author**
- **Do an underpowered trial to accept the null hypothesis**
- **Use self laudatory language in describing your trials (eg, definitive, unique, landmark)**

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Marks of good trials

- **Randomized**
- **Adequate sample size**
- **Meaningful outcome measure**
- **Adequate period of followup**
- **Analysis by original treatment assignment**
- **Adequate bias control procedures**
- **Adequate performance**

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Essential counting and analysis rules

Study population

- **Count as enrolled when randomized**
- **Count as randomized when assignment revealed to clinic**
- **Count in treatment group to which randomized, regardless of subsequent course of treatment and followup, including dropouts and noncompliant patients**

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Essential counting and analysis rules (cont'd)

Count of events

- **Count from time of randomization forward, ie, count regardless of when an event occurs after randomization and initiation of treatment**
- **Count all higher order events (eg, deaths in an MI study) even if treatment not expected to have effect on such events**
- **Count events separately before combining to create a composite outcome measure**

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Essential counting and analysis rules (cont'd)

Analysis principles

Basic principle: The initial comparison of treatment groups should include all patients assigned to the respective treatment groups, should be by original treatment assignment, and should include all recorded events for the outcome of interest

- **Primary analysis should be by original treatment assignment; include all patients randomized and outcomes observed regardless of course of treatment or time from randomization**
- **For trials not involving death as the primary outcome: comparisons for higher order outcomes should be performed before proceeding to the comparison of primary interest**
- **Comparisons for individual events or outcome measures should be performed before presenting analyses for a composite event or outcome measure**

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Telltale clues regarding rule violations

- **Absence of specific statements regarding counting or analysis principles employed**
- **Unexplained varying denominators**
- **Telltale words in the abstract or methods, such as "evaluable" patients**
- **Large differences in baseline comparability of the groups**
- **Large departures from the expected assignment ratio**

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The title

- **Informative, short, and succinct**
- **Use of key design terms such as trial and randomized**
- **Communicates something about the treatments being evaluated and the disease or population under study**

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The abstract

- **Second only to the title in importance**
- **The best abstracts are short, succinct, and structured**
- **A good abstract should provide the following statements or facts**
  - **Purpose of study**
  - **Study treatments (control and test treatments)**
  - **Level of treatment masking**
  - **Method of treatment assignment**
  - **Number of patients enrolled (total and per treatment group)**
  - **Length of followup**
  - **Primary outcome measure**
  - **Main result**
  - **Conclusion**

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Design

- **Adequacy of bias control procedures**
- **Method of treatment assignment and vulnerability to abuse**
- **Adequacy of separations, especially of sponsors with proprietary interests in the outcome**
- **Data analysis independent of the sponsor, especially for sponsors with proprietary interest in the outcome**
- **Independent treatment monitoring board**

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Methods

- **Method of bias control, especially in relation to masking**
- **Method of treatment assignment**
- **Landmark event defining enrollment of a person into the trial**
- **Method of ongoing monitoring**
- **p-value philosophy in relation to multiple looks and subgroup analyses**
- **Statement of counting and analysis principles**

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Analysis

- **Was the outcome measure of primary interest selected prior to the start of data collection?**
- **Are higher order events and outcomes analyzed? before the event or outcome of interest?**
- **If the focus is on a subgroup was the subgroup identified by data dredging?**
- **Are differences in the baseline composition of the treatment groups taken into account in the analysis?**
- **Why are the results being reported now?**

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Tables and figures

- **Should convey essence of results without having to read text**
- **Titles should be succinct**
- **Figures should be crisp (ie, worth 1,000 words; not 1,000 words of explanation)**
- **Tables should provide numerator and denominator data**

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Referencing

Should be:

- **Extensive and complete**
- **Primary**
- **Accurate**
- **Accessible**

(8:36am Thursday) 22 April 2004 **\Reading\Refs**

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Looking for that which is not there

- **Reading the fine print of footnotes**
- **Credits and acknowledgments**
- **Sources of support**
- **Affiliations and conflict of interest disclosures**
- **Absences of statements regarding counting and analysis principles**

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Validity vs generalizability

- **Validity and generalizability are different concepts**
- **A comparison from a trial is valid so long as there is a legitimate basis for comparison of the different treatment groups**
- **Design maneuvers such as randomization, masking, and standardized data collection procedures are all designed to help ensure valid treatment comparisons**
- **The ability to generalize requires a sampling frame (usually absent by definition in the clinical trial setting) or must be done on the basis of judgment**

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Non-issues

- **Lack of representativeness**
- **Inability to define the population from which patients were recruited**
- **The size of the population approached for study not agreeing to study**
- **Minor imbalances in the treatment groups**
- **Minor changes in procedures over the course of the trial**
- **Departures from normal practice procedures**
- **The lack of perfection**

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Remember

- **Criticism is easier than craftsmanship**
- **There are no perfect studies -- only imperfect ones**
- **No one sets out to do a bad study**
- **Receiving criticism can be painful**

(8:22am Thursday) 22 April 2004 **\Reading\Remember**

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Universal criticisms

- **Wrong study population**
- **Study population not representative of general patient population**
- **Conclusions not valid or irrelevant because of select nature of study population**
- **Study groups not comparable at entry**
- **Sample size or length of followup inadequate**
- **Treatment difference (or lack of one) accounted for by unidentified subgroup of patients**
- **Data collection or processing errors**
- **Important data overlooked in collection or analysis**
- **Wrong or inadequate analyses**
- **Wrong treatments or method of administration**
- **Wrong or inadequate diagnostic or evaluation procedures**
- **Results of the trial are not clinically relevant**

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Myths and misconceptions

- **The randomization process is invalid if there are significant differences among the treatment groups with regard to one or more baseline characteristics**
- **Results of the trial should be ignored if there is a difference in the baseline comparability of the treatment groups**
- **The failure to find a significant treatment difference should lead to acceptance of the null hypothesis**
- **Unmasked trials are invalid**
- **Conclusions should be based only on an outcome measure clearly identified as such before initiation of the trial**
- **Marked heterogeneity of the study population makes it impossible to draw conclusions from the trial**

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10 questions for readers

1. **Was the trial done under a legitimate state of equipoise?**
2. **Are the investigator trustworthy?**
3. **Do I believe the investigators to be free of financial and philosophical conflicts of interest in regard to the treatments under evaluation?**
4. **Did the authors adhere to the principle, *once randomized always counted*?**
5. **Is there reason to believe all events (outcomes) observed have been counted and in the treatment group to which patients were assigned regardless of course of treatment?**

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10 questions for readers (cont'd)

6 Did the design include adequate provisions for bias control?
7 Are variations in denominators for treatment comparisons explained and are the explanations consistent with good practice principles of trials?
8 Do the authors recognize and discuss potential weaknesses of their design and execution?
9 Is the primary analysis by original treatment assignment (intention to treat)?
10 Have the authors done adequate analyses to explain their results?

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10 questions for readers (cont'd)

The ultimate question

Do I believe the results to be reproducible in spite of weakness in the study design and execution?