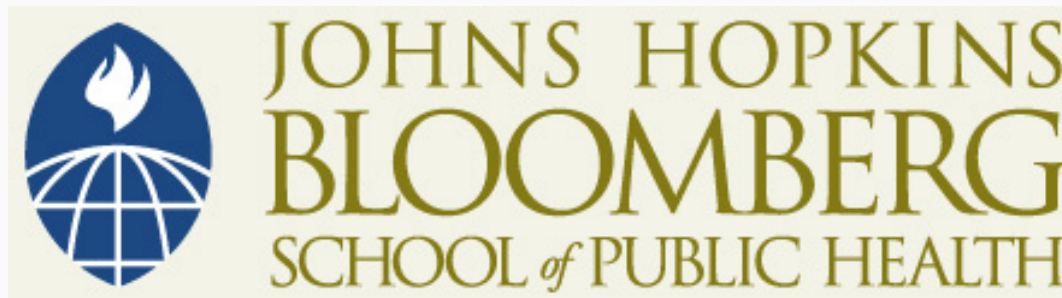


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Analysis Issues, ITT, Post-Hoc, and Subgroups

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Section A

Intention to Treat

Intention to Treat

- The principal is that every patient who is randomized should be included in the analysis
- Why
 - Ensures a valid analysis; ensures different groups of patients are comparable (because of randomization)
 - Avoids many causes of bias; particularly avoids ambiguous decisions about who to include/who not to include in the analysis

Intention to Treat

- Which treatment is better?
or . . .
- Is treatment X better than treatment Y?
 - “Better” as used in “clinical practice” or “all other things being equal?”

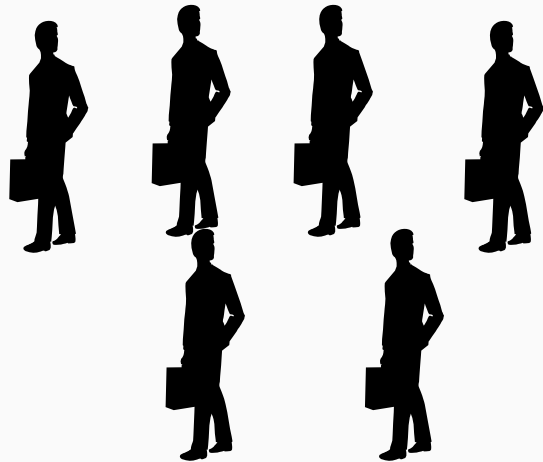
Which Treatment is Better, Treatment X or Y?

- Who wants to know the answer?
 - Pharmaceutical company/producer
 - Regulators
 - Prescribers
 - Purchasers
 - Patients

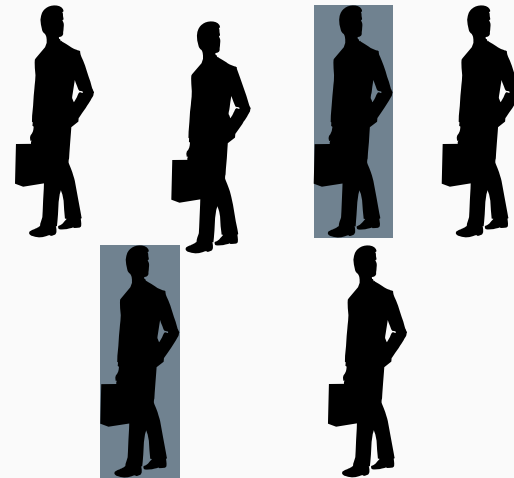
Intention to Treat

Medical vs. Surgical Treatment for Operable Tumours

Medical Treatment



Surgical Treatment



Five-Year Mortality Rates According to Compliance

	Treatment Group A		Treatment Group B (Placebo)	
Compliance	No Pats	% Mortality	No Pats	% Mortality
< 80%	357	24.6%	882	28.2%
> 80%	708	15.0%	1813	15.1%
Total	1065		2695	

Complete Follow-Up (On All Patients)

- Implications of complete follow-up
- Pragmatism (intention to treat [ITT]) answers the question: “what is the outcome if my policy is to use treatment X?”
 - Does this make sense with placebos?

Intention to Treat

- Pragmatism (pragmatic implantation of ITT)
- All randomised patients
- Not necessarily all recruited patients
- Not necessarily all treated patients (but usually)
- “All randomised patients with at least one post-baseline (questions on-treatment) efficacy assessment”
- **All randomised patients!**

Guidelines on “Statistical Analysis of Clinical Studies”

- Investigatory trials
 - Only subjects eligible for entry into the trial who have completed the present trial in accordance with the protocol should be strictly selected and [analysed]
- Practical trials
 - In the case of practical trials, on the other hand, it is also claimed that the subjects who have undergone the trial treatment should be included in analysis regardless of duration of treatment [and analysed] even if there is no possibility that they will show up . . . as being “improved” (ITT)

- FDA guidelines for “The Format and Content of the Clinical and Statistical Sections of New Drug Applications”
 - As a general rule, even if the applicant's preferred analysis is based on a reduced subset of the patients with data, there should be an additional “intent-to-treat” analysis using all randomized patients

- “Biostatistical Methodology in Clinical Trials for Marketing Authorisations for Medicinal Products”
 - In general, it is advantageous to demonstrate a lack of sensitivity of the principal trial results to alternative choices of patient population for analysis
 - When the ITT and the per protocol analyses come to essentially the same conclusions, confidence in the study results is increased

- “Structure and Content of Clinical Study Reports”
 - As a general rule, even if the applicant's preferred analysis is based on a reduced subset of the patients with data, there should be an additional “intention-to-treat” analysis using all randomized patients

- “Statistical Principles for Clinical Trials”
 - The guideline introduced a new idea with the name: the “full analysis set”
- Decisions concerning the analysis sets should be guided by the following principles:
 1. To minimise bias
 2. To avoid inflation of type I error

- “Statistical Principles for Clinical Trials”
 - In many clinical trials, the use of the full analysis set provides a conservative strategy
 - There are a limited number of circumstances that might lead to excluding randomised subjects from the full analysis set

In the Next Section We'll Look at . . .

- Subgroup analyses
 - Post-hoc analyses
 - Unreliable conclusions



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Section B

Analysis Issues

Subgroups and Post-Hoc Analysis

- We've already seen one example of subgroups of "compliant" vs. "non-compliant" patients

Five-Year Mortality Rates According to Compliance

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Compliance	No Pats	% Mortality	No Pats	% Mortality
< 80%	357	24.6%	882	28.2%
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Total	1065		2695	

Uncertainty in Data

- We can never know the “truth”
- So we make estimates and draw conclusions that are . . .
 - Hopefully reliable
 - Inevitably not certain
- One analysis; one chance of making a mistake
- Multiple analyses; multiple chances for error (and they tend to “add up”)

Five-Year Mortality Rates According to Compliance

	Treatment Group A		Treatment Group B	
Compliance	No Pats	% Mortality	No Pats	% Mortality
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- Why “compliance” as the subgroup?
- Why not age, metabolic rate, co-morbidity, etc.?
- Why this “cut-off” (80%) for compliance?

A Priori Analysis Plan

“Still, it is an error to argue in front of your data. You find yourself insensibly twisting them around to fit your theory.”

—*Sherlock Holmes (via Sir Conan Doyle) in
The Adventure of Wisteria Lodge*

A Priori Analysis Plan

- So one solution is to pre-specify every detail:
 - What the subgroups will be
 - What the “cut-off” criteria will be (if any)
- It is then equally important to report every analysis

So-Called “Fishing Expeditions”

- Searching through the data, hoping to find “something interesting”
- “Fishing expedition . . . the analogy of dipping a fishing rod into dark water and pulling out various items of rubbish, but rarely fish!”*

Further Problems with Subgroups

- Too many “statistically significant” differences
- Not enough “statistically significant” differences

Too Many “Differences”

- Because the probability of each “statistically significant difference” not being real is 5%
- So lots of 5%s all add together
- Some of the apparent effects (somewhere) will not be real
- We have no way of knowing which ones are and which ones aren't

Not Enough “Differences”

- The concept of “power”
- The probability of detecting a real effect, if one exists
- The more data we have, the higher this probability (the higher the “power”)
- But sub-group analyses “cut the data”

Not Enough “Differences”

- Trials are expensive!
- We usually fix the size of the trial to give high “power” to detect important differences overall
- When we start splitting the data (only look at men; or only look at women; or only look at renally impaired; or only look at the elderly; etc., etc.), the sample size is smaller . . . the power is much reduced

So What's Going On?

1. Too many “statistically significant” differences
2. Not enough “statistically significant” differences
 - These two problems are both at work simultaneously and we have little (or no) idea which effects to believe in and which not to

In the Next Lecture We'll Look at . . .

- Missing data
 - Reasons
 - Problems
 - Bias
 - Solution