Multiplicities

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Summary

- Multiplicities are everywhere
- They are responsible for wasting vast amounts of clinical trial resources
- Always interpret everything in context
- PRESPECIFY!!

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Definition? At least a possibility…

- Testing multiple hypotheses at the same time
- Testing the same hypothesis multiple times

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Prototypical example

- Trial does not meet its primary endpoint
- Investigators look at 30 different subgroups and endpoint variants
  - Find something significant
  - Finally, we knew the treatment worked, we just didn't know how or for who…now we do!
- Run another trial…result is NOT confirmed…UGH!

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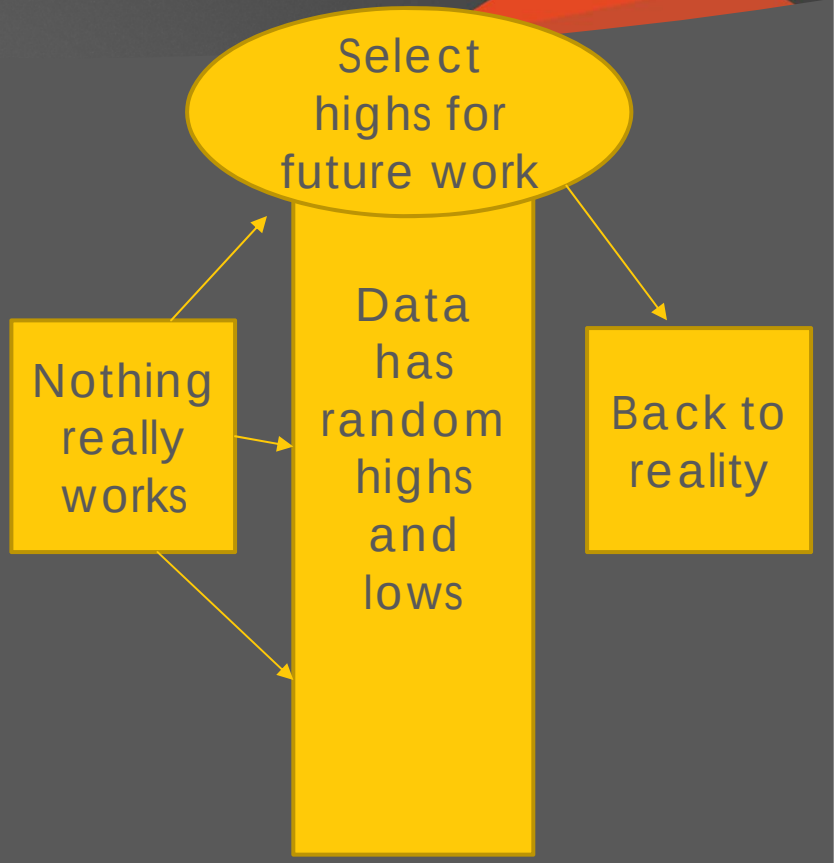
What happened?

- All statistical tests have a possibility of a false positive.
- Test enough things, and something will be significant.



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What's wrong with this picture?

- Simple design
  - See if you have significant at N=100
  - If not, check again at N=200
  - If not, check again at N=300
  - and so on....

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Subtleties

- I consult on historical borrowing
  - utilizing historical data in clinical trials
  - you must have ”good data” to do this. Biases are bad.
- Someone brought me historical data from one of their trials, and wanted to use it in phase 3
  - phase 3 would be in the same population as this dataset
  - we proceeded to work through a design (my mistake!)

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Subtleties

- Eventually, I asked the right question
  - "what other data did you look at?"
- The data they gave me was just a subset
  - they had many other subgroups
  - they looked through them, and decided to run phase 3 in the most promising subgroup
  - this is biased!

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Subtleties

- We prepare phase 3 trials
  - Most have good phase 2 data.
- Should that be taken at face value?

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Corrections for Multiplicities

- The hardest thing is RECOGNIZING multiplicities
- Post-hoc analyses are impossible to quantify
  - what might you have looked at?
- Analyses should be prespecified
  - Clear description of the number and kind of analyses, and how multiplicities are to be addressed

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Corrections for Multiplicities

- Corrections like Bonferroni are the simplest.
- If you have 5 tests, divide your 2.5% and test each using 0.5%
  - chance of making ANY error controlled at 2.5%

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Corrections for Multiplicities

- There are well defined solutions for multiple interim analyses
- O'Brien Fleming, alpha spending functions.
  - These take into account the correlation between interims, so the nominal alpha total is greater than 2.5%

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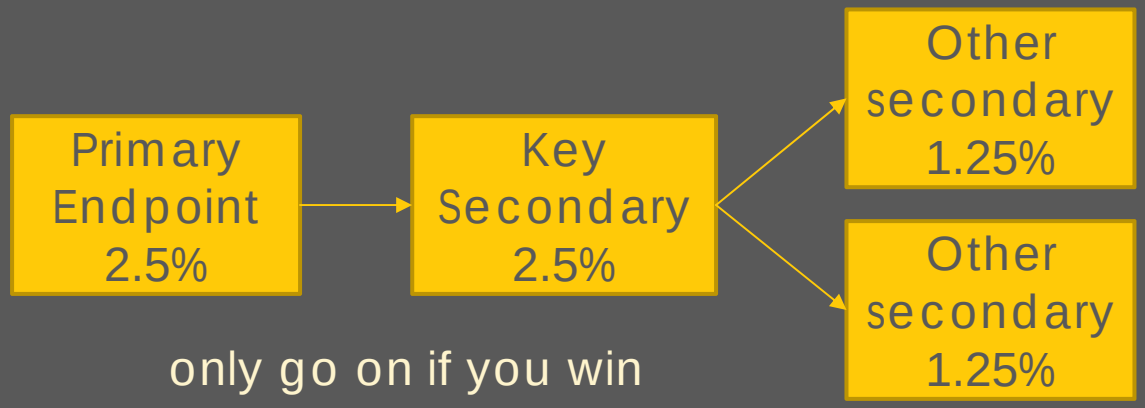
Corrections for Multiplicities

- Gatekeeping
- If some analyses are more important, test those first.
  - only test remainder if first ones are significant
  - pick wisely!



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False discovery rates

- For lots of tests (for example genetic data), you cannot avoid making any mistake.
- Instead of controlling the probability of any mistake, control the proportion of incorrect decisions
  - e.g. 90% of claimed successes are true
- This depends on the true underlying rates

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What ifs?

- Do old statisticians have any type I error left?

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What ifs?

- Master protocols investigate
  - the same compound in multiple indications, OR
  - different compounds in a single indication

- Should there be a correction for this?

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Summary

- PRESPECIFY ANALYSES
- Specify how you handle the resulting multiplicity
- Consult your friendly local statistician for clever possibilities

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