Statistics for Clinical Trials: Basics of a Phase III Trial Design

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Conflicts

- Family member works for Roche Canada and owns stock
- Received honorarium (DSMB) from Takeda

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Phase III RCTs

1. Two-arm, double-blind, superiority RCT
2. Cross-over
3. Biomarker-enriched
4. Biomarker stratified
5. Equivalence / Non-inferiority
6. Factorial
7. Bayesian adaptive
8. Dynamically allocated randomization
9. …

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Outline

1. Randomization
2. Blinding / Concealment
3. Intention-to-treat
4. Statistical Power (α and β)
5. P-values / Confidence Intervals

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What is Randomization?

- The most fundamental principle in statistics
- Ensures comparability of interventions
- Non-deterministic process by which patients assigned to intervention
- All patients have same chance of getting each treatment

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Statistical Importance

- Patient cohorts become similar / balanced as sample size get large
- Balanced: known and *unknown* characteristics
- Observed difference (outcomes) due to treatment effect / imbalance in characteristics / chance
- Chance can be quantified

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Statistical Interpretation

- Median survival for patients given A > median survival for patients given B by 6 months

- Prob(due to chance) = XX (say 0.002)

- Prob(baseline imbalance) = Prob(due to chance)

- Prob(treatment effect)=?, however, chance is unlikely => assume treatment effect

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Problems

- True randomization balances as sample sizes get large
- Many clinical trials have small sample sizes
- Unequal # of pts allocated to each arm (cost, feasibility)
- Imbalance in characteristics (credibility)

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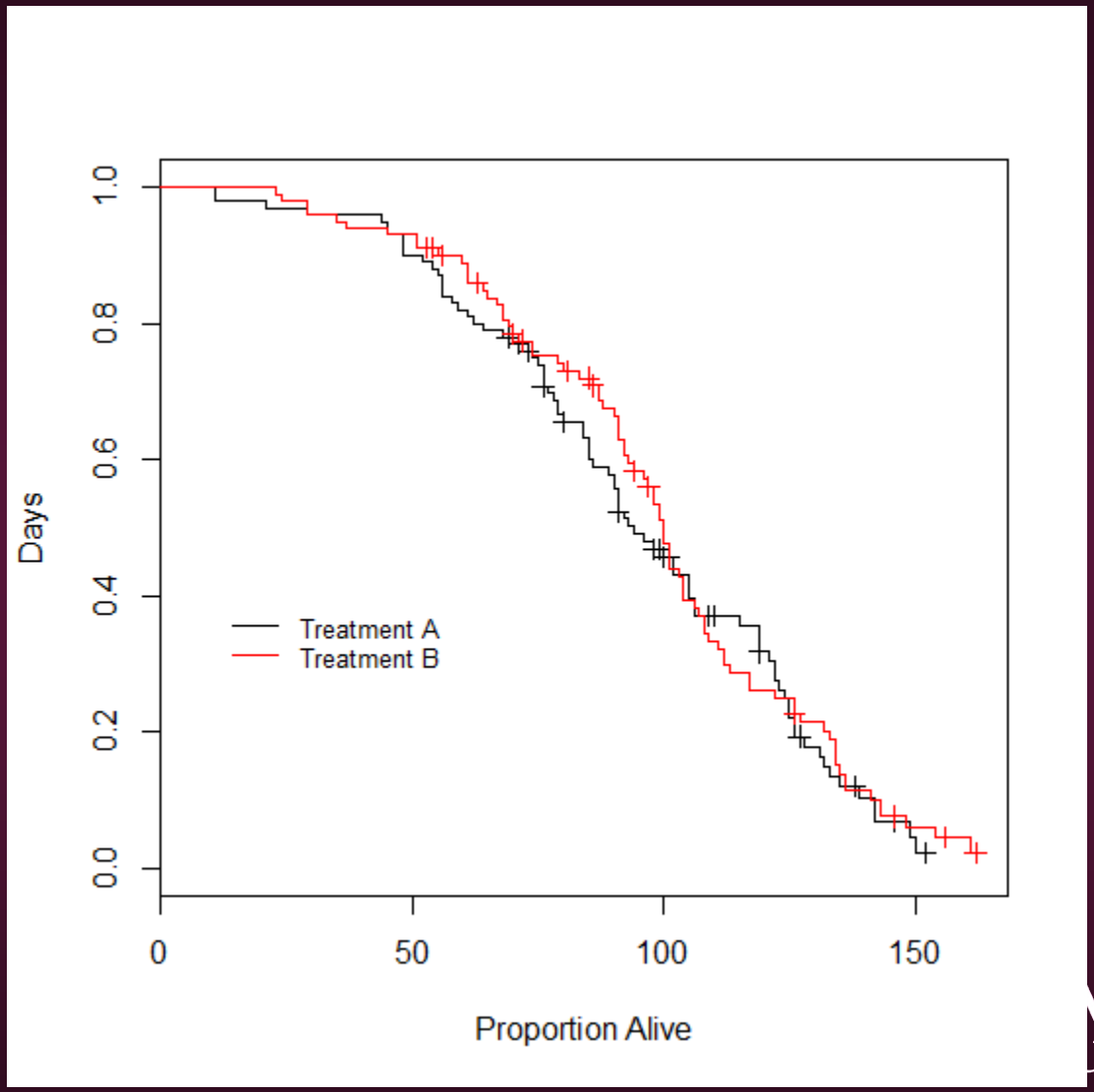

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Quasi-Randomization

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Quasi-Randomization

- Permuted Blocks Random Sampling
- AABB, ABBA, ABAB, BBAA, BAAB, BABA
- Randomly select a block
- Ensures approximately equal numbers of patients get each treatment

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Quasi-Randomization

- Stratified Random Sampling
- Select ‘stratification factors’ of importance
- Permuted blocks within strata
- Ensures approximately even number of patients within each stratum receive each treatment

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Dynamic Allocation

- Often referred to as minimization
- Evaluate characteristics of patients already on study
- Allocate next patient to treatment which will create better balance
- e.g. if 10 women received A and 7 received B, then the next woman allocated to B

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Blinding / Concealment

- Important that researchers do not know next allocation
- If I know permuted blocks used, and last three patients were AAB, then I know next patient is B
- I may (sub)consciously (not) recommend trial to next patient
- Bias trial results

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Subconscious Example

- Organize clinic so easier cases earlier in the day
- Personal belief that A is easier to tolerate (despite community equipoise)
- Know next patient will get B
- May be less likely to present trial to complex patient at end of day (7 PM)

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Terminology

- Concealment – ensuring people are unaware of next treatment allocation

- Blinding – ensuring people are unaware of treatment patient is receiving

- Reduces ability to 'guess' next treatment

- Reduces bias caused by process changes (e.g. schedule changes / conmeds)

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Blinding Terminology

- Single blind – patients do not know treatment (surgery trials)
- Double blind – patients and physicians blinded
- Triple blind – adjudicators blinded also (radiologist); May change treatment incorrectly
- Reduces bias, but less similar to real life

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Blinding considerations

- Must consider ability to blind
- Surgery vs oral medication
- Will toxicities unblind allocation?
- How does blinding affect future treatments?

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Intent-to-Treat Principle

- All patients randomized should be analyzed according to *allocation*

- Patient randomized to surgery (experimental arm). Opts to withdraw and gets oral medication (control arm)

- Analyzed on surgery arm

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Intent-to-Treat Principle

- More conservative analysis. E.g. assume all patients cross over and get same treatment. Treatment effect is 0.

- ITT biases towards no difference. Hence, if H0 rejected, we have strong evidence to do so.

- Reduces bias due to perceived / true lack of blinding

- Preserves planned statistical power

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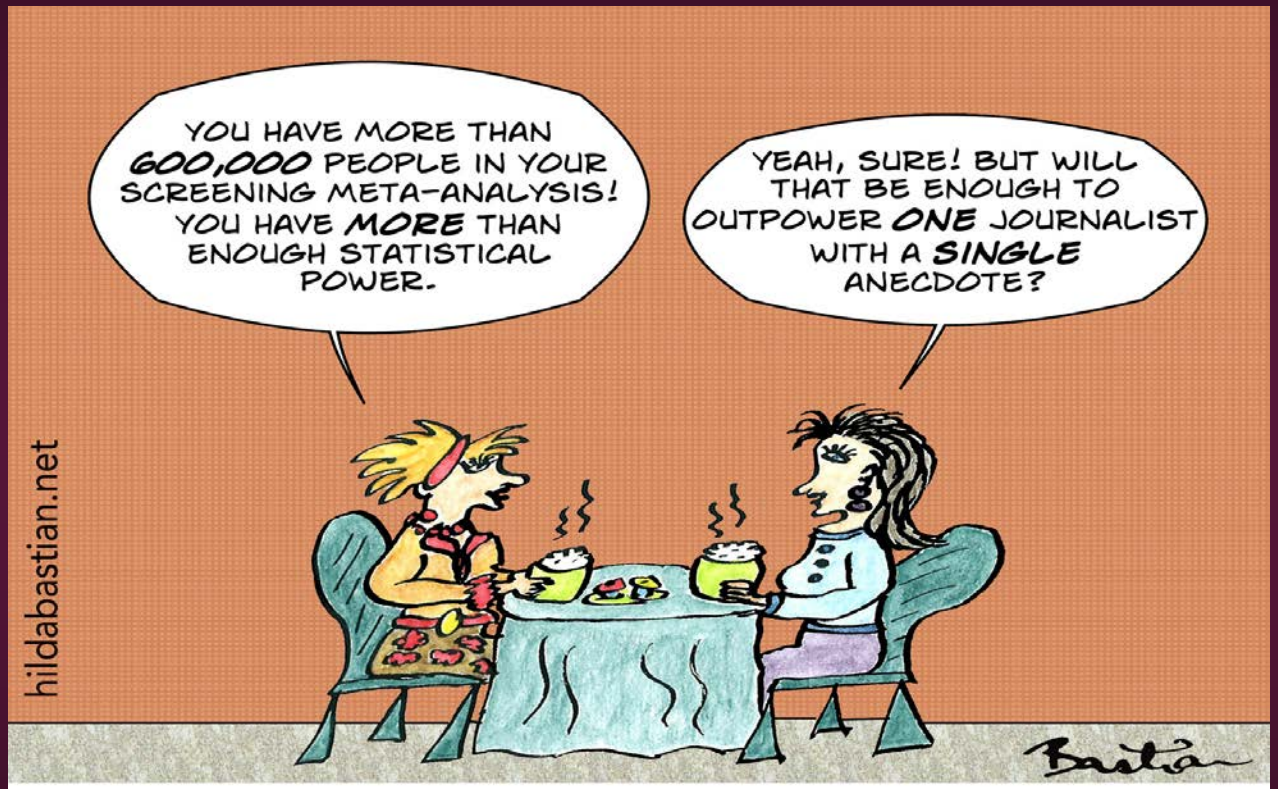
Statistical Power



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Error Rates

- α is the probability, *assuming H0 is true*, that we will reject H0
- *If drug is inactive*, α is the probability our study will conclude the drug is active
- β is the probability, *assuming HA is true*, that we will not reject H0
- *If drug is active*, β is the probability our study will conclude the drug is inactive
- Power is (1-β)*100%

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Statistical Errors

	Truth is H0	Truth is HA
Study Conclusion is H0 is True	Study is Correct	β, type II
Study Conclusion is HA is True	α, type I	Study is Correct

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Statistical Errors

	Truth is H0	Truth is HA
Study Conclusion is H0 is True	Study is Correct	β, type II
Study Conclusion is HA is True	α, type I	Study is Correct

At study conclusion, only information available

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Designing a Study

- Want to increase chance of making a correct decision
- For fixed sample size, if α decreases, β increases
- To decrease α and β, must increase sample size
- Sample size calculation is the minimum number required so that both α and β are ≤ some 'reasonable value'

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Why α=0.05, β=0.20?

- No statistical motive, but 'works'
- α error: Truth is novel agent is inactive

=>Further study in phase III, patient/financial costs

- β error: Truth is novel agent is active

=>Not studied again, lost a potentially useful treatment

- Weigh relative cost of each error

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P-values

- P-values: Probability, assuming H0 is true, of observing data as extreme or more extreme, than what actually was observed if trial was repeated identically many times

- NOTE: there is an ongoing debate amongst statisticians whether p-values should be reported or not!

Problems with p-values

- Does not say it is true, just it is plausible
- 'we do not have enough evidence to reject H0"

- Low p-values do NOT mean H0 is false
- Assumption: probability is low

=>unlikely to occur by chance

=>more likely that H0 is false

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Problems with p-values

- P-values of 0.051 is not really different than p-values of 0.049

- Except p=0.049 gets a better publication

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P-values are probabilities

- Probabilities have different meanings, depending on the context

- Assume patient has positive test result from a diagnostic test, false-positive rate=0.01

- Then take a second test which is negative, and false-negative rate=0.0000001

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Confidence Intervals

- Range of values of which the data are consistent
- If H0 is any value within a 95% CI, then the p-value would be ≥0.05
- It does NOT mean the true value is in CI
- If trial repeated many times – 95% of identically constructed CI will cover true value

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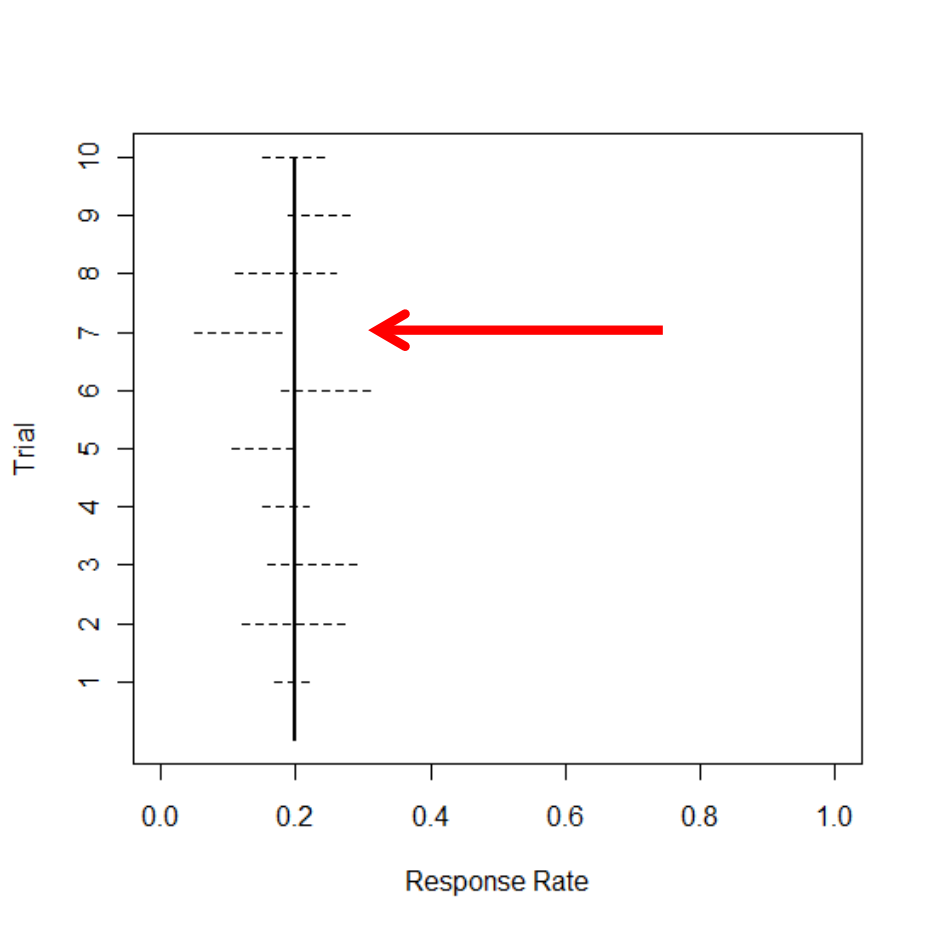
Confidence Intervals



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Subgroup Analyses

- Are there particular subpopulations which demonstrate effect?

- Be cautious – do not over-interpret

- Remember, if H0 is true, $\alpha=0.05$ means 1 of 20 tests significant *by chance alone*

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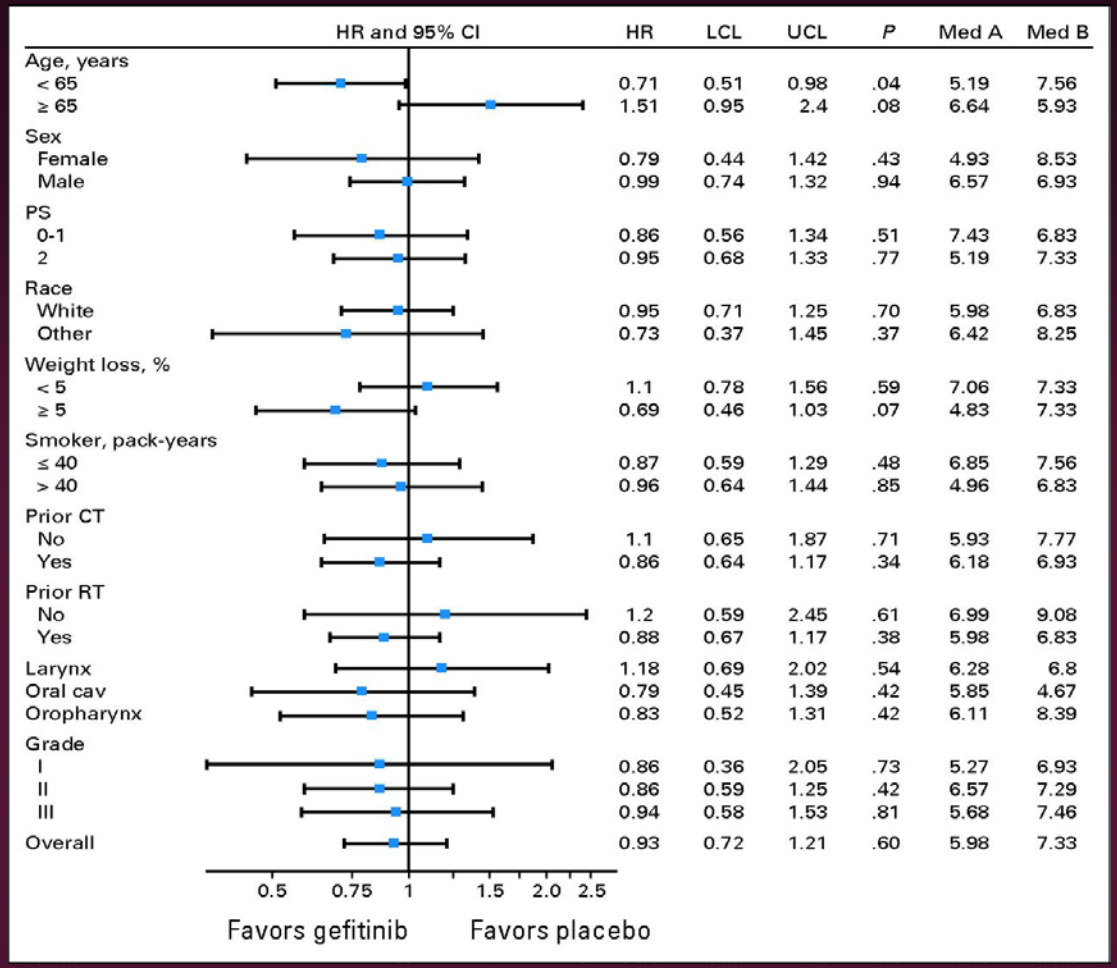

Results: In an unplanned subgroup analysis, we found that patients younger than 65 years derived survival benefit from combination therapy (median OS, 7.6 months with docetaxel/gefitinib *v* 5.2 months with docetaxel/placebo; $P = .04$).

Conclusion: Our observation of a potential survival benefit with the addition of gefitinib to docetaxel in younger but not older patients may warrant further validation in clinical studies.

NOTE: 22 tests in H&N cancer – plausible? HPV (?) Mutations (?)

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Argiris et al. JCO 31(11); April 2013, doi: 10.1200/JCO.2012.45.4272

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