

Posch-Bauer Seamless Test

Antonio Nieto / Javier Gómez



Agenda

- Adaptive design.
- Seamless design.
 - Type I and type II error.
 - Multiplicity.
- Closed Testing Procedure.
 - Posch Bauer method.

Adaptive Design



- It is becoming a common tool in clinical development programs.
- A design that involves the option of implementing modifications in the design, based on the results of an interim analysis.
- It speeds up the clinical development program of a compound, while maintaining statistical and regulatory standards.

Types of Adaptive Designs

Most common:

- Group-sequential designs.

A classical standard design where interim/futility analyses are specified to proof efficacy before the end of the trial.

- Sample size reassessments.

Used when uncertainty in the treatment effect is present and the effect is clinically relevant at the interim analysis, but the desired power with the current sample size is not achieved.

but there are others

Seamless Design



It is usually referred as a phase II/III clinical trial.

- First part (phase II design), where several dose/schedule levels of a experimental arm and control arms are investigated.
- Second part (phase III design), where the experimental arm and the control arm are properly compared.

Advantages.

- Phase II joined with phase III information to obtain a more robust and powerful conclusion from the comparison.
- No long break between the phase II and phase III stages occurs in the clinical development program.

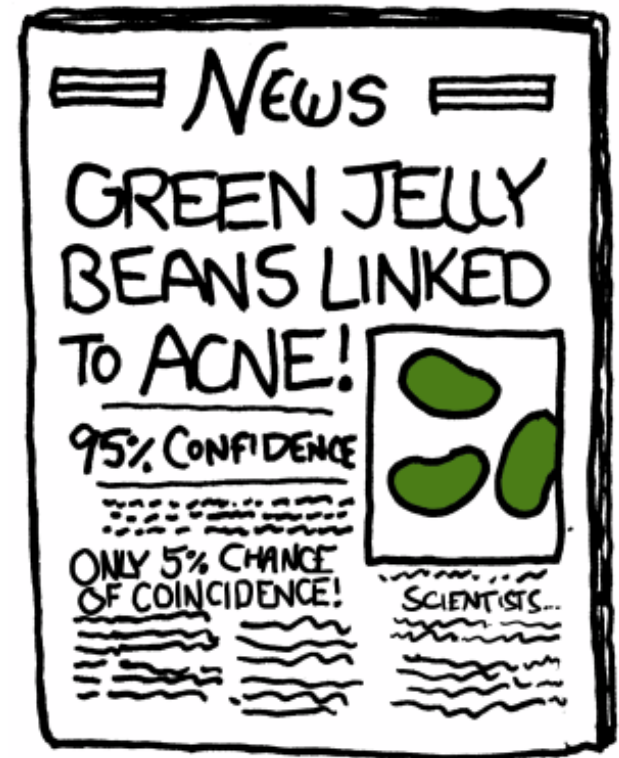
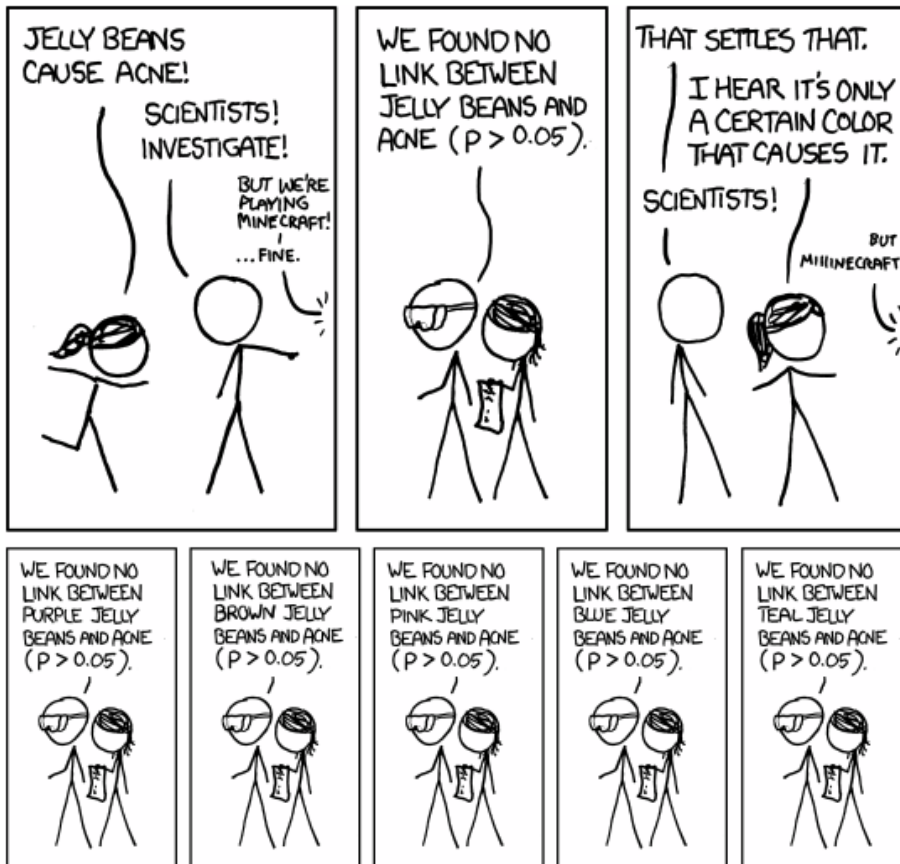
Type I and Type II Error

- **Type I error** occurs when one rejects the null hypothesis when it is true (probability of type I error; α =significance level).
- **Type II error** occurs when one rejects the alternative hypothesis (fails to reject the null hypothesis) when the alternative hypothesis is true (probability of type II error; β).

		Reality	
		The null hypothesis is true	The alternative hypothesis is true
Research	The null hypothesis is true	✓	Type II error
	The alternative hypothesis is true	Type I error	✓

- **Power (1- β)** is the probability to find in the sample an effect that really exists in the population (i.e. the “sensitivity” of the test).

Typical Example



Inflation Type I Error

- Multiplicity: This refers to the fact that the more tests you conduct, the more likely you are to claim you have a significant result when you should not have (commit type I error).

- $\alpha^* = 1 - (1 - \alpha)^n$

- Example: Doing all possible 95% pairwise comparisons on five means (i.e., 10 comparisons) $\Rightarrow$

$$\alpha^* = 1 - (1 - \alpha)^{10} = 1 - (1 - 0.05)^{10} = 1 - 0.599 = 0.401$$

Bonferroni's Correction

- Developed by Italian mathematician Carlo Emilio Bonferroni.
- Highly conservative method.
- If n tests are performed, each of them with probability α' , then the probability that at least one of them comes out significant is $\leq n\alpha'$
- So solving then $\alpha' = \alpha/n$
 - Example: Doing all possible 95% pairwise comparisons on five means (i.e., 10 comparisons) then $\alpha' = 0.05/10 = 0.005$

Closed Testing Procedure

- Suppose the overall type I error rate is α and k hypotheses $H_1, \dots, H_k$ to be tested.
- The closed testing principle allows the rejection of any one of these elementary hypotheses (H_i), if all possible intersection hypotheses involving H_i can be rejected by using valid local level α tests.
- It controls the familywise error rate in the strong sense for all the k hypotheses at level α .

Closed Testing Procedure (II)

- Suppose there are three hypotheses H_1, H_2 , and H_3 to be tested and the overall type I error rate is 0.05.
- H_1 can be rejected at level α if:

- $H_1 \cap H_2 \cap H_3$,
 - $H_1 \cap H_2, H_1 \cap H_3$
 - and H_1
- } all are rejected with level 0.05

Posch-Bauer Method (Example)

- Run a four-arm phase II trial (stage 1).
- Run a second two-arm phase III trial using the selected dose (stage 2).
- Use the data from both parts (stage 1+ stage 2) to evaluate the treatment's effectiveness.

EXAMPLE

Reject $H^{(1)}$ and conclude that dose group 1 is superior to placebo if all of the following conditions are satisfied

1. $C(p_1, q_1) \leq \alpha$
2. $C(p^{(1,2)}, q^{(1,2)}) \leq \alpha$
3. $C(p^{(1,3)}, q^{(1,3)}) \leq \alpha$
4. $C(p^{(1,2,3)}, q^{(1,2,3)}) \leq \alpha$

Posch-Bauer Method: Combining p-values

- Let p and q be respective p-values for testing any null hypothesis H over two stages.
- Form a combination function. The inverse normal combination function is

$$C(p, q) = 1 - \Phi \left[\sqrt{\frac{N_1}{N_1 + N_2}} \Phi^{-1}(1 - p) + \sqrt{\frac{N_2}{N_1 + N_2}} \Phi^{-1}(1 - q) \right]$$

where N_1 and N_2 are sample sizes for Stages 1 and 2-

- Reject the hypothesis if

$$C(p, q) < \alpha$$

Summary



- Adaptive designs (including Seamless) are good statistical methods for clinical development.
- But type I error and multiplicity have to be controlled at all times.
 - Bonferroni is an alternative, but not the only one.
- Closed Testing Procedure (Posch-Bauer Seamless Test) is one of the best solutions to control multiplicity and gives us a good method to combine p-values.
 - SAS macro is available at the paper.

Questions

