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Trial Design and Statistical Analysis of Immune Response to Combination Vaccines

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**Regulatory guidance: 21 CFR
601.25 (d) (4) (ii)**

“A biological product may combine two or more safe and effective active components: . . . (ii) when combining of the active ingredients does not decrease the purity, potency, safety, or effectiveness of any of the individual active components; and. . . . “

Design Translation of 21 CFR 601.25 (d) (4)
(ii)

- **Aim regarding effectiveness: to demonstrate that combining antigens into a single injection does not reduce efficacy by a clinically meaningful amount, for each vaccine component**
- **Concern is one-directional: no reason to limit superiority of combination vaccine**
- **Non-inferiority (one-sided equivalence) trials**

Efficacy Endpoints

- **Usually not cases of disease, esp. if components are previously licensed or their efficacy has been previously demonstrated**
 - **disease incidence may be too low due to widespread use of separate vaccine components**
 - **foreign clinical-endpoint efficacy trial may be done, but bridging study still needed**
- **Measures of immune response used as correlates of protection (not as easy to understand as clinical endpoints)**

Immune Response Endpoints

- **geometric mean concentrations (GMCs)**
- **proportions responding in a pre-specified manner**
 - **for Hib: post-vaccine anti-PRP antibody concentration**
 - ≥ **0.15 µg/ml (correlate of short-term protection?)**
 - ≥ **1.00 µg/ml (correlate of long-term protection)**

Hypotheses

- **Alternative: what the trial aims to demonstrate (non-inferiority of combination by clinically meaningful amount)**
- **Null: the complement of the alternative (combination is inferior by a clinically important amount)**
- **Design trial to reject (not demonstrate) null hypothesis**

Consequence of hypotheses: error probabilities have usual meaning

- **Type I (α): prob. of rejecting null when it is true (claiming non-inferiority when comb. is inferior)**
- **Type II: prob. of not rejecting null when it is false (failing to demonstrate non-inferiority when combination is truly non-inferior)**

GMCs (μ_{comb} , μ_{sep}): Hypotheses

For each component:

$$H_0: \theta = \mu_{comb} / \mu_{sep} \leq \theta_0$$

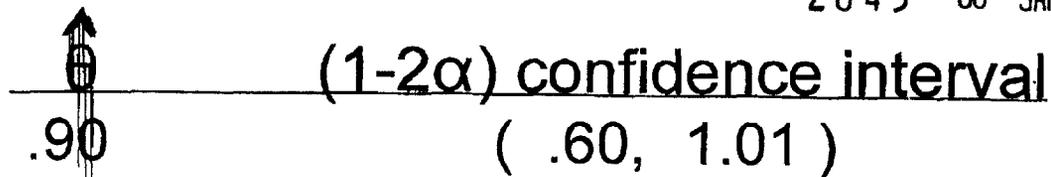
$$H_a: \theta = \mu_{comb} / \mu_{sep} > \theta_0$$

★ Choice of θ_0 : .5 ? .66 ? ?

★ What is clinically meaningful?

GMCs (μ_{comb} , μ_{sep}): Analysis

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- CI is for θ , a ratio (comparative, not individual, in nature)
- Lower limit is important one (because combination is in numerator of ratio)
- Does lower limit exceed θ_0 ? If so, conclude H_a : combination is not inferior.
- (1-2 α) CI provides a test of size $\leq \alpha$
 - if tail probabilities are equal

Difference in Proportions Responding: Hypotheses

For each component:

$$H_0: \delta = P_{comb} - P_{sep} \leq -\delta_0$$

$$H_a: \delta = P_{comb} - P_{sep} > -\delta_0, \text{ for } \delta_0 > 0$$

- ★ Choice of δ_0 : .25? .15? .10? .05? ?
- ★ Should δ_0 be the same for antibody $\geq 0.15 \mu\text{g/ml}$ and $\geq 1.0 \mu\text{g/ml}$ anti-PRP?
- ★ Should δ_0 be different for different target populations?

Difference in Proportions Responding: Analysis

$$\hat{\delta} \quad (1-2\alpha) \text{ confidence interval}$$

0.4 (- .08, .10)

- Lower limit important one
(combination minus separate)

- Does lower limit exceed $-\delta_0$?
 - If $-\delta_0$ is $-.10$, then reject H_0
(conclude combination is not inferior to separate)

 - If $-\delta_0$ is $-.05$, then do not reject H_0 (conclude combination might be inferior)

Issues

- Choice of α : .05 ? .025 ?

$\alpha = .05$ corresponds to 90% CI

$\alpha = .025$ corresponds to 95% CI

- Multiplicity: comparisons for multiple antigens
- Choice of θ_0 and δ_0

What is clinically meaningful?

Reliable immune correlate helpful.

Immunological “creep”