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A method for incorporating historical information in non-inferiority trials

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Outline

▷ Comparative trials: experimental (e) vs control (c)

▷ **Active control** c available ⇒

- Goal: show Non-Inferiority (**NI**) of e vs c
- **Historical information** h on the control from previous studies
- Borrowing information may improve accuracy of estimates, *if current and historical data are homogeneous*

▷ **Problem:**

- what if h is heterogeneous or overwhelming?

▷ **Proposal:**

- A *dynamic power prior* in which the level of borrowing depends on a posterior measure of compatibility between c and h

Methodology

▷ Model assumptions

- θ_j: probability of success $j = e, c$
- X_j: random number of responses out of n_e
- $X_j|\theta_j \sim Bin(n_j, \theta_j)$, $j = e, c$
- $X_e \perp X_c \,|\, \theta_e, \theta_c$

▷ NI test formulation

- $H_0: \; \theta_e - \theta_c \leq -\delta$ vs $H_1: \; \theta_e - \theta_c > -\delta$

  with $\delta > 0$ prefixed NI margin

▷ Prior construction and posterior derivation

- *no prior information for* θ_e: $\pi_0^e(\theta_e) = Beta(1, 1)$

  $\Rightarrow \pi_0^e(\theta_e|x_e) = Beta(1 + x_e, 1 + n_e - x_e)$

- *historical information* (x_h, n_h) *for* θ_c: power prior (see [9])

  $\pi_P(\theta_c|x_h) \propto \pi_0(\theta_c) \times [f(x_h|\theta_c)]^{a_0}, \quad a_0 \in [0, 1]$

  $\Rightarrow \pi_P(\theta_c|x_h, x_c) = Beta(1 + a_0 x_h + x_c, 1 + a_0(n_h - x_h) + n_c - x_c)$

▷ Choice of a_0

- $a_0 = 1 \quad \Rightarrow$ **full borrowing**
- $a_0 \in (0, 1) \Rightarrow$ **partial borrowing**
- $a_0 = 0 \quad \Rightarrow$ **no borrowing**

▷ NI test conclusion

- $C = [L, U]$: credible interval for $\theta = \theta_e - \theta_c$ (via Monte Carlo)
- If $L > -\delta$, then H_0 is rejected, i.e. e is **not inferior** to c.

Idea: how to choose a_0

Choose a_0 is a measure of agreement between the two posteriors $\pi_0^c(\cdot|x_c)$ and $\pi_0^h(\cdot|x_h)$ based on the non informative priors $\pi_0^c(\cdot)$ and $\pi_0^h(\cdot)$

$$a_0(x_c, x_h) = \int_{S(x_h)} \pi_0^c(y|x_c) dy,$$

where $S(x_h)$ is a $(1-\gamma)$-credible set for θ_c wrt. $\pi_0^h(\cdot|x_h)$. The stronger the consensus, the larger the value of a_0 in the power prior.

Motivating example

NI study described in [10] to compare a pentavalent vaccine (RotaTeq) with a placebo against Rotavirus. Data are the number of subjects in the two groups with positive response to vaccination.

Study	Arm	j	n_j	x_j	$\hat{\theta}_j = x_j/n_j$
Current	*Experimental*	e	558	415	0.74
	Control	c	592	426	0.72
Historical	*Control*	h	483	367	0.76

Table 1: Current data for both experimental and control arms and historical data on the control, obtained by combining four different studies using a meta-analytic model.

Real data show that $\hat{\theta}_c < \hat{\theta}_h$ (scenario (a)). For comparison, two fictitious scenarios are considered: (b) $\hat{\theta}_c = \hat{\theta}_h = 0.72$, (c) $\hat{\theta}_c > \hat{\theta}_h = 0.68$. Table 2 illustrates the impact of the dynamic choice of a_0 on the posterior probability of H_1 $P(H_1|x_c, x_e)$, in contrast with full borrowing ($a_0 = 1$) and no borrowing ($a_0 = 0$) of historical information.

Historical data		a_0	L	U	$U - L$	$P(H_1\|x_c, x_e)$
		1	**-0.039**	0.050	0.089	0.944
(a) *Real*	$\hat{\theta}_h > \hat{\theta}_c$	0.486	**-0.035**	0.058	0.093	0.964
		0	-0.028	0.075	0.103	0.982
		1	-0.024	0.068	0.092	0.989
(b) *Fictitious*	$\hat{\theta}_h = \hat{\theta}_c$	0.970	-0.024	0.068	0.092	0.988
		0	-0.027	0.076	0.103	0.981
		1	-0.006	0.085	0.091	0.999
(c) *Fictitious*	$\hat{\theta}_h < \hat{\theta}_c$	0.587	-0.012	0.083	0.095	0.996
		0	-0.027	0.076	0.103	0.981

Table 2: Credible intervals (bounds and length) for $\theta = \theta_e - \theta_c$ and posterior probability of $H_1: \theta > -\delta = -0.03$ for different choices of a_0 and historical data.

▷ Comments

(a) historical data strenghten H_0: the larger a_0 the smaller $P(H_1|x_c, x_e)$;

(b) high compatibility between c and h ⇒ limited effect of borrowing;

(c) historical data favour H_1: the larger a_0 the larger $P(H_1|x_c, x_e)$.

▷ Frequentist properties: type-I error and power

As required by regulatory agencies [1] evaluation of the method in terms of Type-I error rate α and power $\eta(\theta)$ is reported in Table 3.

(a)				(b)				(c)			
a_0	α	ξ	$\eta(\theta)$	a_0	α	ξ	$\eta(\theta)$	a_0	α	ξ	$\eta(\theta)$
1	0.002	0.05	0.268	1	0.015	0.05	0.571	1	0.081	0.05	0.825
		0.1	0.967			0.1	0.996			0.1	1.000
0.486	0.019	0.05	0.392	0.931	0.020	0.05	0.562	0.587	0.065	0.05	0.673
		0.1	0.974			0.1	0.993			0.1	0.986
0	0.025	0.05	0.480	0	0.025	0.05	0.480	0	0.025	0.05	0.480
		0.1	0.975			0.1	0.975			0.1	0.975

Table 3: Empirical Type-I error rates and powers for different values of ξ under scenarios (a), (b) and (c), given $\delta = 0.03$, $n_e = 558$, $n_c = 592$, $\theta_c^\star = 0.72$, for different levels of a_0.

References

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