Sample Size Considerations for Japanese Patients in a Multi-Regional Trial Based on MHLW Guidance

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Outline

- Bridging study to Multi-regional clinical trial (MRCT)
- PMDA guidance
- Normal endpoint
- Survival endpoint
- Simulation Results
- Examples
- Discussion

From Bridging study to MRCT

- Differences in ethnicity, culture and clinical practice may have impact on efficacy, safety and dose regimen
- Duplications of large clinical trials in all regions demand resources and delay the approvals of new drugs.
- ICH E5 issued in 1998 recommends a framework for evaluating ethnical impact
  - Conduct Bridging study to show evidence of similarity
  - Extrapolate data from the original region to a new region

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From Bridging study to MRCT (2)

- No standard for bridging studies: no statistical criteria to assess similarity of two populations
  - Shih (2001): predictive probability of new data falling within the previous experience
  - Chow et al (2002): sensitivity index and bioequivalence approach
  - Hsiao et al. (2003): GS technique for internal validity assuming sequential data availability
- In Japan: similarity criteria to be set on a case-by-case basis through a PMDA consultation

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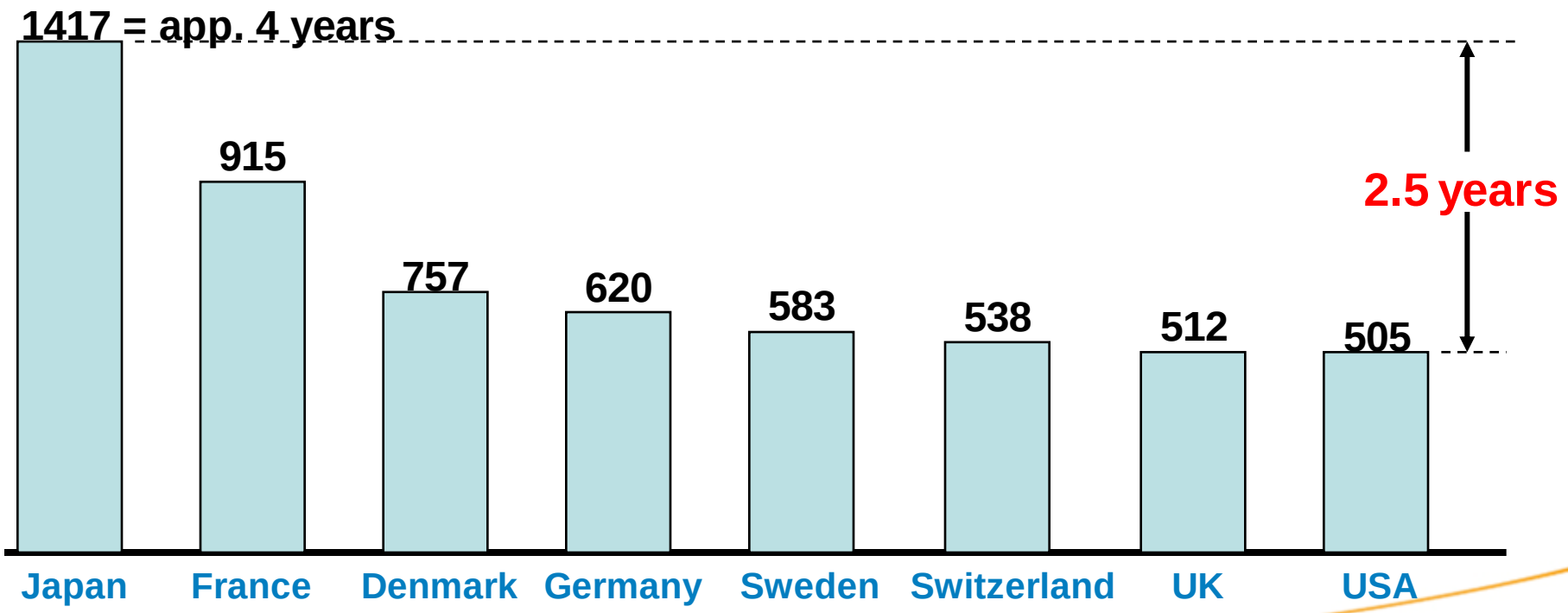
From Bridging study to MRCT (3)

- Since ICH E5, new drug approvals in Japan based on bridging strategy increased from 3.2% in 1999 to 25% in 2003
- However, bridging studies were often after new drug's approval in the original region
- Availabilities of new drugs to Japanese patients were delayed

“Drug lag” in Japan

Days from first approval in the world to launch in each country
(average of top 100 products)



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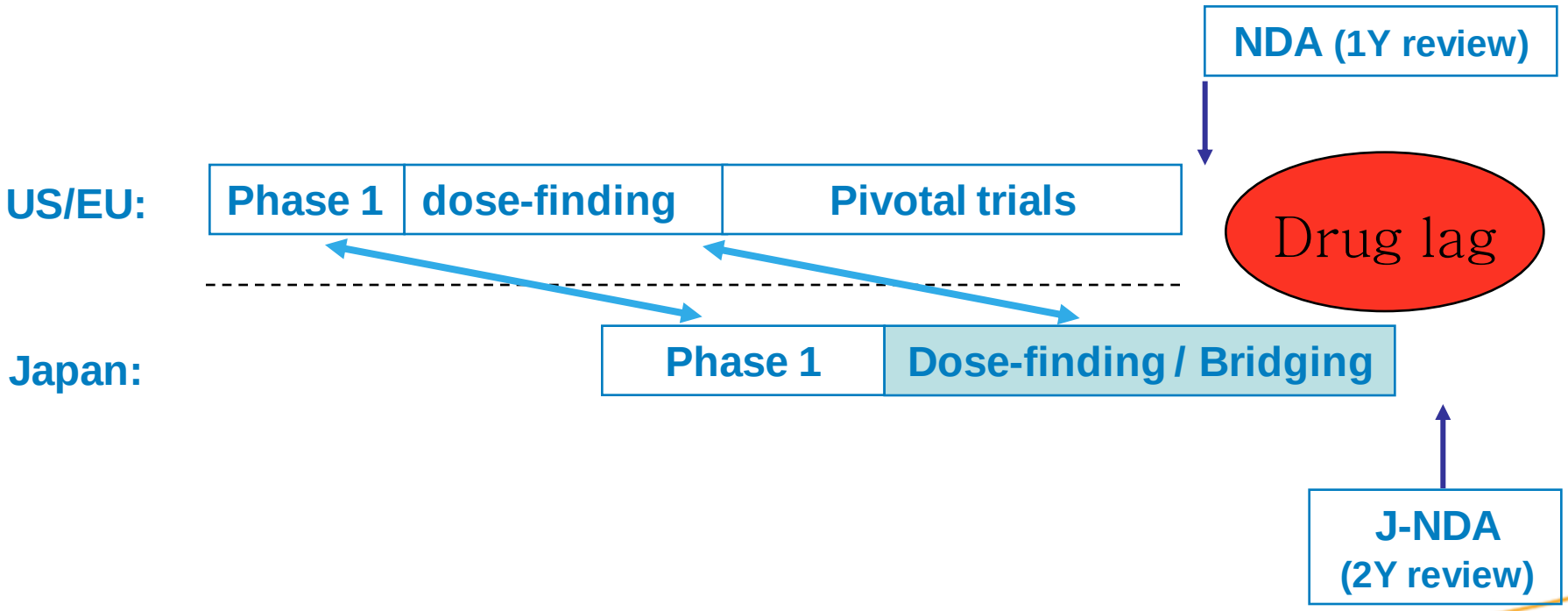
Bridging Strategy

- The bridging study is often a dose ranging study



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PMDA dual approach:

- PMDA issued a new guidance in September 2007
  - To Promote Japan's participation in multi-regional (Global) clinical trials to shorten sponsor's drug development time in Japan
  - In a Q&A format
  - Q6 is specifically for assessing consistency of treatment effects
- PMDA planned to shorten the review time
  - Increase PMDA reviewers from 90 to 300 by 2011
  - Decrease review time from 21 months to 12 months by 2011
    - Reviewers 9 months / sponsor 3 months
- Overall, reduce drug lag (time between overseas and Japan approvals) from 4.3 years to 1.5 years by 2011

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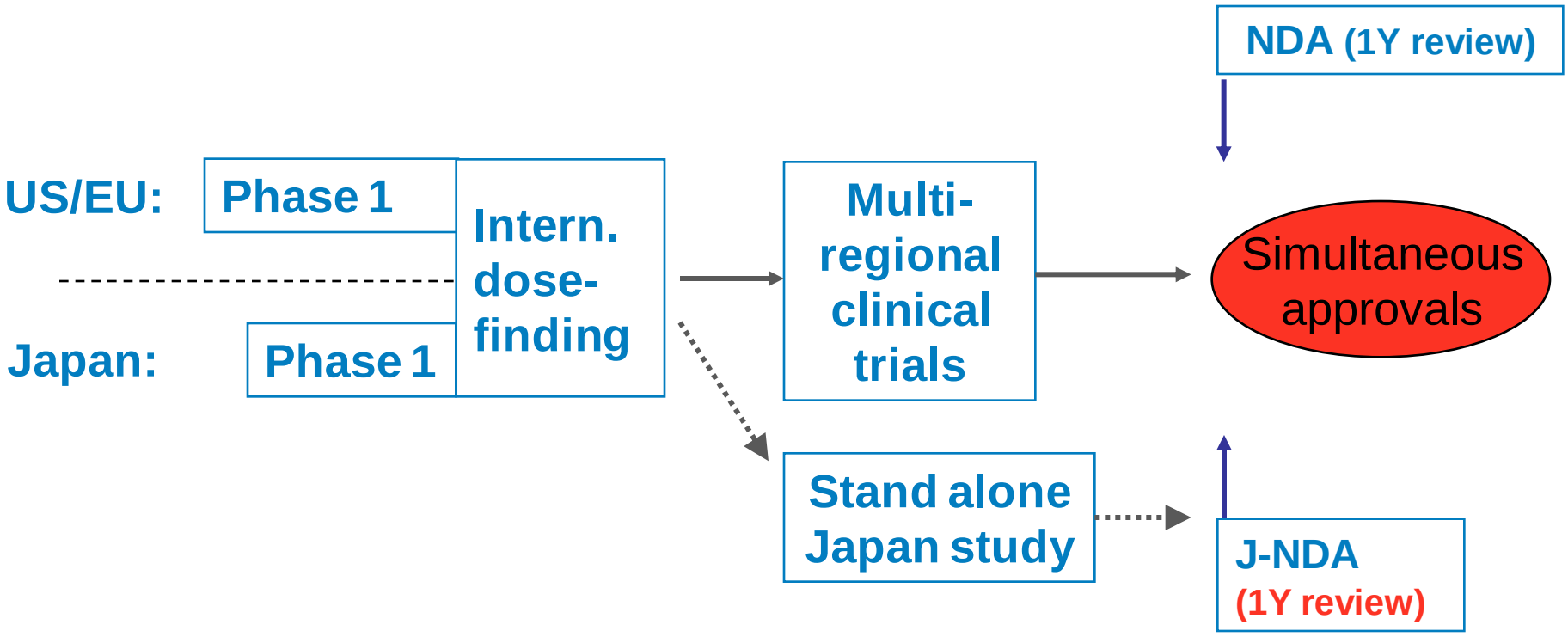
MRCT towards Simultaneous submissions



- Start Japan development earlier
- Reduce J-NDA review timelines

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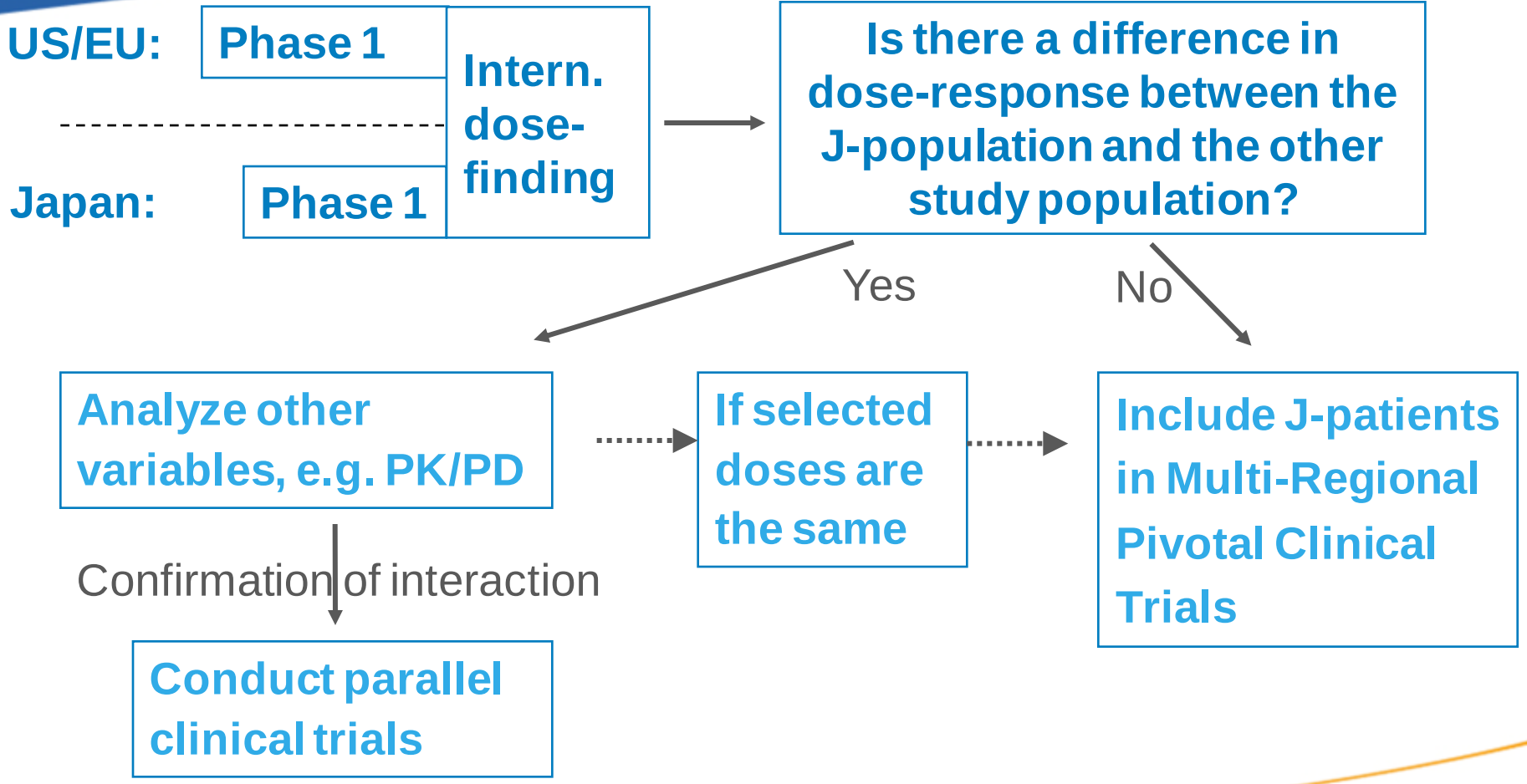
Key decision point about MRCT



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PMDA Guidance on MRCT

- No recommendation of any definitions for consistency, but two methods were provided as examples (superiority trials, Non-inferiority trials?)
- Method 1: Enough Japanese patients for

  $Pr(D_{Japan}/D_{all} > \pi) = 1-\beta' \geq 0.8$ and $\pi \geq 0.5$

  - Observed non-inferiority
  - Not H_0: $\delta_{JP} < \pi\delta$ vs H_a: $\delta_{JP} \geq \pi\delta$
- Method 1: Sekiguchi et al. (JSM, 2007) using simulation for a MR oncology trial.

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PMDA Guidance on MRCT (2)

- Method 2: Enough patients in all regions for

  $\Pr(D_1>0, D_2>0, D_3>0)=1-\beta' \geq 0.8$

  - lack of observed qualitative interaction
- Method 2: Kawai et al. (DIJ, 2007)

The focus here: Method 1

- A systematic and comprehensive discussion on sample size calculations
- Closed form formulas for normal, binary and survival endpoints.

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Normal Endpoint

For $1-\beta$ power and α level two-sided test, the overall

$$N = \frac{2\sigma^2 (z_{\alpha/2} + z_{\beta})^2}{\delta^2}$$

Then

$$\hat{\delta}_{all} = (N_J \hat{\delta}_J + N_{NJ} \hat{\delta}_{NJ}) / N$$

Suppose treatment effects $\delta_J = u\delta_{NJ}$ and f_u is the fraction of Japanese patients ($N_{uJ} = f_u N$)

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Normal Endpoint (2)

For

$$\Pr(\hat{\delta}_J > \pi\hat{\delta}_{all} \mid \delta_J, \delta_{NJ}) = 1 - \beta'$$

We have

$$z_{\beta'} = \frac{(z_{\alpha/2} + z_\beta)\sqrt{f_u}(u - \pi - \pi(u-1)f_u)}{(1+(u-1)f_u)\sqrt{1+(\pi^2 - 2\pi)f_u}}$$

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Normal Endpoint (3)

If u=1 or $\delta_J = \delta_{NJ}$, a closed form solution

$$f_1 = \frac{z_{\beta'}^2}{(z_{\alpha/2} + z_\beta)^2(1-\pi)^2 + z_{\beta'}^2(2\pi - \pi^2)} \uparrow \text{of } \pi$$

Treating $\hat{\delta}_{all}$ as a fixed δ

$$\Pr(\hat{\delta}_J > \pi\delta \mid \delta_J = \delta_{NJ} = \delta) \geq 1 - \beta'$$

We have

$$N_J = \frac{2\sigma^2 z_{\beta'}^2}{\delta^2(1-\pi)^2} = \frac{z_{\beta'}^2 N}{(z_{\alpha/2} + z_\beta)^2(1-\pi)^2} = f_1' N > f_1 N$$

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Normal Endpoint (4)

Table 1. Values of $f_{0.9}$, f_1, $f_{1.1}$, $f_1^{'}$ (α=0.05)

π	$1-\beta$	$1-\beta'$	$f_{0.9}$	f_1	$f_{1.1}$	$f_1^{'}$
0.5	0.90	0.80	0.290	0.224	0.174	0.270
0.5	0.95	0.80	0.248	0.187	0.143	0.218
0.5	0.90	0.85	0.383	0.313	0.253	0.409
0.5	0.95	0.85	0.334	0.265	0.209	0.331
0.5	0.90	0.90	0.494	0.426	0.361	0.625
0.5	0.95	0.90	0.437	0.367	0.303	0.506
0.6	0.90	0.80	0.396	0.311	0.240	0.421
0.6	0.95	0.80	0.349	0.265	0.198	0.341
0.6	0.90	0.85	0.496	0.416	0.340	0.639
0.6	0.95	0.85	0.444	0.360	0.285	0.517
0.6	0.90	0.90	0.603	0.537	0.467	0.977
0.6	0.95	0.90	0.549	0.475	0.401	0.790

Normal Endpoint (5)

To have a positive trial and satisfy MHLW requirement, consider

$$\Psi = \Pr(\hat{\delta}_J - \pi\hat{\delta}_{all} > 0, \hat{\delta}_{all} - z_\alpha \sigma / \sqrt{N/2} > 0 \mid \delta_J = \delta_{NJ} = \delta)$$

Correlation $\rho = \dfrac{z_{\beta'}}{z_{\alpha/2} + z_\beta} > 0$, $\Psi \approx> (1-\beta)(1-\beta')$

The conditional probability

$$\Pr(\hat{\delta}_J - \pi\hat{\delta}_{all} > 0 \mid \delta_{all} - z_\alpha \sigma / \sqrt{N/2} > 0, \delta_J = \delta_{NJ} = \delta) \approx 1-\beta'$$

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Normal Endpoint (6)

Table 2. Values of ρ and Ψ (α =0.05)

π	$1-\beta$	$1-\beta'$	$(1-\beta)(1-\beta')$	ρ	Ψ^*
0.5	0.90	0.80	0.720	0.260	0.735
0.5	0.95	0.80	0.760	0.233	0.768
0.5	0.90	0.85	0.765	0.320	0.781
0.5	0.95	0.85	0.808	0.288	0.816
0.5	0.90	0.90	0.810	0.395	0.826
0.5	0.95	0.90	0.855	0.356	0.864
0.6	0.90	0.80	0.720	0.260	0.735
0.6	0.95	0.80	0.760	0.233	0.768
0.6	0.90	0.85	0.765	0.320	0.781
0.6	0.95	0.85	0.808	0.288	0.816
0.6	0.90	0.90	0.810	0.395	0.826
0.6	0.95	0.90	0.855	0.356	0.864

Normal Endpoint (7)

For imbalanced design, *N* for placebo and *kN* for active treatment, replace

$$2\sigma^2 \quad \text{by} \quad \frac{k+1}{k}\sigma^2$$

Actually, f_u and f_1' are independent with *k*

For binary endpoint, replace

$$2\sigma^2 \quad \text{by} \quad p_1(1-p_1)+p_0(1-p_0)$$

Survival Endpoint

Consider Proportional Hazards model

$$\lambda_1(t) = \lambda_0(t)e^{\gamma}$$

The power is often based on log rank test

$$T \sim N(\mu,1) \quad \text{and} \quad \mu = \gamma\sqrt{E}/2$$

where *E* is the expected total number of events of 2 groups.

$$\hat{\gamma} = 2T/\sqrt{E} \sim N(\gamma, 4/E)$$

For power $1-\beta$,

$$E = \frac{4(z_{\alpha/2} + z_{\beta})^2}{\gamma^2}$$

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Survival Endpoint (2)

There are 4 approaches depending on what asymptotic distributions are used for

$$\Pr\left(\frac{1-e^{\hat{\gamma}_J}}{1-e^{\hat{\gamma}_{all}}} > \pi \mid \gamma_J, \gamma_{all}\right) \geq 1-\beta' \quad (*)$$

Difficult to calculate the correlation between $\hat{\gamma}_J$ & $\hat{\gamma}_{all}$ if pooled data are used for $\hat{\gamma}_{all}$

Consider $\hat{\gamma}_{all} = w\hat{\gamma}_J + (1-w)\hat{\gamma}_{NJ} \quad (0 \leq w \leq 1)$

Note that, this is for design not for analysis

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Survival Endpoint (3)

When $w = E_J / E$, weight=inverse of the variance and

$$Var(\hat{\gamma}_{all}) = 4/E$$

is same as the one from the pooled analysis.

Consider the asymptotic distribution for

$$1 - e^{\hat{\gamma}_J} - \pi(1 - e^{\hat{\gamma}_{all}})$$

Suppose $\gamma_J = u\gamma_{NJ}$ and $E_{uJ} = g_u E$. g_u should satisfy

$$\frac{\sqrt{E}(1 - \pi + \pi e^{(ug_u + 1 - g_u)\gamma_{NJ}} - e^{u\gamma_{NJ}})}{2\sqrt{\frac{1}{g_u}e^{2u\gamma_{NJ}} - 2\pi e^{(u(1+g_u)+1-g_u)\gamma_{NJ}} + \pi^2 e^{2(ug_u+1-g_u)\gamma_{NJ}}}} = z_{1-\beta'}.$$

Survival Endpoint (4)

When $\gamma_J = \gamma_{NJ}$, a closed form solution

$$g_1 = \frac{4e^{2\gamma} z_{\beta'}^2}{E(1-\pi)^2(1-e^{\gamma})^2 + 4e^{2\gamma}(2\pi - \pi^2)z_{\beta'}^2}$$

The number of events for Japanese patients

$$E_{1J} = g_1 E$$

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Survival Endpoint (5)

Replace $\hat{\gamma}_{all}$ by γ_{all}. For

$$\Pr\left(\frac{1-e^{\hat{\gamma}_J}}{1-e^{\gamma_{all}}} > \pi \mid \gamma_J = \gamma_{all} = \gamma\right) \geq 1-\beta'$$

the number of events for Japanese patients

$$E_J > \frac{4z^2_{\beta'}}{(\gamma - \log(1-\pi(1-e^{\gamma})))^2} = E_{2J}$$

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Survival Endpoint (6)

As Hung et al. (SIM, 2003), we can also consider asymptotic distribution for

$$\hat{\eta} = \log\left(\frac{1-e^{\hat{\gamma}_J}}{1-e^{\hat{\gamma}_{all}}}\right)(\geq \log\pi)$$

Then, when $w = E_J / E$ in $\hat{\gamma}_{all}$ and $\gamma_J = \gamma_{NJ}$

$$E_{3J} = \frac{4e^{2\gamma} z_{\beta'}^2 E}{E(\log\pi)^2(1-e^{\gamma})^2 + 4e^{2\gamma} z_{\beta'}^2}$$

Or if set $\hat{\gamma}_{all} = \gamma$ in $\hat{\eta}$, $E_{4J} = \frac{4e^{2\gamma} z_{\beta'}^2}{(\log\pi)^2(1-e^{\gamma})^2} > E_{3J}$

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Survival Endpoint (7)

Table 3. Number of Events for Survival Endpoint (α =0.05)

π	$1-e^{\gamma}$	$1-\beta$	$1-\beta'$	E	E_{1J}	E_{2J}	E_{3J}	E_{4J}
0.5	0.2	0.90	0.80	844	156	204	85	94
0.5	0.2	0.95	0.80	1044	160	204	87	94
0.5	0.3	0.90	0.80	330	54	75	29	32
0.5	0.3	0.95	0.80	409	55	75	30	32
0.5	0.4	0.90	0.80	161	23	34	12	13
0.5	0.4	0.95	0.80	199	23	34	12	13
0.6	0.2	0.90	0.80	844	221	312	144	174
0.6	0.2	0.95	0.80	1044	231	312	149	174
0.6	0.3	0.90	0.80	330	77	113	50	59
0.6	0.3	0.95	0.80	409	80	113	52	59
0.6	0.4	0.90	0.80	161	33	51	21	24
0.6	0.4	0.95	0.80	199	34	51	22	24

Survival Endpoint (8)

- Different approaches give very different required number of events
- For the first case, $E_{1J} = 18.5\%E \quad E_{2J} = 24.2\%E$

$$E_{3J} = 10.1\%E \quad E_{4J} = 11.1\%E$$

- Simulation is used to check the coverage

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From number of events to sample size

- Consider a fixed stopping time design: patients enter at staggered time but stop at the same common study end date.
- Expected number of events for Treatment *i*

$$E_i = \frac{r\lambda_i}{\lambda_i + \tau}\left(A - \frac{e^{-(\lambda_i+\tau)L}}{\lambda_i + \tau}\left(e^{(\lambda_i+\tau)A} - 1\right)\right) = rV_i$$

where *A*=enrollment period, r=enrollment rate

τ =dropout rate, *L*=study duration

$$N = rA = AE/(V_0 + V_1)$$

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From number of events to sample size

- Number of Japanese patients can be derived using

$$N_J = AE_J / (V_0 + V_1)$$

- If the Japanese sites are anticipated to be opened later than the other sites, more than N_J Japanese patients are needed to reach E_J when the total number of events for the study reaches *E*.

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Table 4. Probabilities of (*)

(α =0.05, λ_0 =5%, τ = 0 and L=36)

π	$1-e^{\gamma}$	$1-\beta$	$1-\beta'$	E	P_{1J}	P_{2J}	P_{3J}	P_{4J}
0.5	0.2	0.90	0.80	844	0.779	0.826	0.710	0.727
0.5	0.2	0.95	0.80	1044	0.780	0.814	0.715	0.726
0.5	0.3	0.90	0.80	330	0.771	0.815	0.702	0.717
0.5	0.3	0.95	0.80	409	0.774	0.808	0.706	0.714
0.5	0.4	0.90	0.80	161	0.762	0.816	0.698	0.711
0.5	0.4	0.95	0.80	199	0.775	0.808	0.698	0.713
0.6	0.2	0.90	0.80	844	0.791	0.842	0.726	0.752
0.6	0.2	0.95	0.80	1044	0.789	0.831	0.732	0.751
0.6	0.3	0.90	0.80	330	0.782	0.842	0.731	0.752
0.6	0.3	0.95	0.80	409	0.781	0.832	0.725	0.741
0.6	0.4	0.90	0.80	161	0.773	0.839	0.717	0.733
0.6	0.4	0.95	0.80	199	0.775	0.827	0.725	0.732

Example 1 (Continuous endpoint)

- A multi-regional trial to evaluate treatment effect on HbA1c.
- 2:1 imbalanced design for more safety data
- 372 in active treatment and 186 in placebo for 99% power to detect 0.5% difference with SD=1.3% and α=0.05 (two-sided).

Example 1 (2)

Table 5. Sample Size for Japanese Patients in a HbA_{1c} Trial

π	$1-\beta'$	f_1	$f_1^{'}$	N_{1J} via f_1		$N_{1J}^{'}$ via $f_1^{'}$	
				Pbo	Treat	Pbo	Treat
0.5	0.80	0.138	0.154	26	51	29	57
0.5	0.85	0.199	0.234	37	74	43	87
0.5	0.90	0.282	0.358	52	105	67	133
0.6	0.80	0.200	0.241	37	75	45	90
0.6	0.85	0.280	0.365	52	104	68	136
0.6	0.90	0.380	0.559	71	141	104	208

Example 2 (Survival endpoint)

- A multi-regional oncology trial on overall survival
- Median survival time for control=21 months:

$$\lambda_0 = 3.30\%/\text{month}$$

- A hazard rate reduction for treatment of 20%:
- $$\lambda_1 = 2.64\%/\text{month}$$
- Total E=844 for 90% power (two-sided)
- A=42, L=54, τ =0 for mortality ITT analysis
- N=1412

Example 2 (2)

Table 6. Number of Events and Sample Size for Japanese Patients

π	$1-\beta'$	E_{1J}	E_{2J}	E_{3J}	E_{4J}	N^*_{1J}	N^*_{2J}	N^*_{3J}	N^*_{4J}
0.5	0.80	156	204	85	94	261	342	142	158
0.5	0.85	221	310	122	143	370	518	205	239
0.5	0.90	306	474	174	219	512	792	291	366
0.6	0.80	221	312	144	174	370	522	241	291
0.6	0.85	301	473	201	263	503	791	336	441
0.6	0.90	397	723	273	403	664	1210	456	674

Discussion

- The trend is moving away from bridging study to MRCT
- Method 1 in the guidance focuses on observed consistency (observed non-inferiority) for superiority trial.
- Closed form formulas are available for all types of endpoints
- For normal endpoint, mininum=22.4% of total sample size
- It may be prudent to include selected East Asian nations
- How the consistency should be defined for non-inferiority trials if no between-treatment difference is assumed?
- For Method 1?
- For method 2: D1> Δ, D2> Δ, D3> Δ

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