Assessment of consistency of treatment effects in MultiRegional Clinical Trials (MRCTs)
&
Sample size considerations for Japanese patients in a multi-regional trial based on MHLW guidance

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Outline

- **INTRODUCTION**
  - Regulatory environment – Main challenges to the trial community
  - PhRMA MRCT Cross-Functional Key Issue Team (KIT)
- **CORE PRESENTATION**
  - Part I: Assessment of Consistency of Treatment Effects in MRCTs
  - PART II : Sample size considerations for Japanese patients in a multi-regional trial based on MHLW guidance
- **KEY MESSAGES TO TAKE HOME**

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Regulatory environment 1/5

REGULATORY GUIDANCE: WHAT DO WE HAVE ?

- ICH E5 (International Conference on Harmonization Tripartite Guidance) : Ethnic Factor in the Acceptability of Foreign data (1998)
- European Medicines Agency (EMA); Reflection paper on the extrapolation of results from clinical studies conducted outside Europe to the EU-population (draft). EMEA Doc Ref CHMP/EWP/692702/2008. February 2009
- Ministry of Health, Labour and Welfare (MHLW) of Japan. Basic Concepts for Joint International Clinical Trials. September 2007

Presentations by regulators - As an example:

- Hung HMJ. Design considerations for bridging clinical trials and global clinical trials. Presented in DIA Annual Meeting, Atlanta, June 2007

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Regulatory environment 2/5

- ICH E5 (1998) – Key points 1/2:
  - **Objective**: facilitate the registration of medicines among ICH regions (i.e. USA, Europe, Japan) by recommending a framework for evaluating the impact of ethnic factors upon a medicine's effect
  - When there is evidence that differences in ethnic factors could alter the efficacy or safety of the medicine in the population in the new region, the sponsor may need to generate a limited amount of clinical data in the new region in order to extrapolate or "bridge" the clinical data between the two regions
  - Acceptability of the foreign clinical data component depends upon whether it can be extrapolated to the population of the new region
  - Characterization of a medicine as "ethnically insensitive" in terms of PK and PD properties is key AND clinical effects in different regions must be compared

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Regulatory environment 3/5

- **ICH E5 (1998) – Key points 2/2:**
  - Definition of **Bridging** study: study performed in the new region to provide PK-PD or clinical data in the new region that will allow extrapolation of the foreign data to the population in the new region
  - Depending on the context, sometimes a single PK bridging study and/or a bridging study using a short-term pharmacologic endpoint may be sufficient
  - Bridging strategy must be anticipated and discussed on a case-by-case basis with the regulatory authority of the new region

Regulatory environment 4/5

- **EMEA Reflection paper (2009) - Key points:**
  - A complement to the ICH E5
  - Provides a classification of intrinsic (Genetic and Physiological / pathological conditions) and extrinsic (environmental) ethnic factors
  - The paper highlights examples of mainly extrinsic factors that may complicate the extrapolation of results from clinical studies between geographical areas worldwide, as well as within the European population

Regulatory environment 5/5

- **MHLW guidance in Japan (2007) - Key points:**
  - New drug approvals in Japan based on the bridging strategy have been increasing
  - To further streamline and expedite new drug development in Japan, the Ministry of Health, Labour and Welfare recently issued the 'Basic Principles on Global Clinical Trials' guidance to promote Japan's participation in multi-regional trials
  - The guidance provides two methods as examples for recommending the number of Japanese patients in a multi-regional trial.

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PhRMA MRCT Cross-Functional Key Issue Team (KIT)

- Formed in 2008
- Composed of sponsor's representatives including Sanofi-Aventis
- Objective: address the challenges and fully realize he opportunities of MRCTs
- One of the work streams focused on the assessment of consistency of treatment effects across regions
- Publication was a main objective of that work stream:
  - Paper published in Pharmaceutical Statistics, 2009
  - Paper accepted for publication in Drug Information Journal in March 2010
- A Sanofi-Aventis technical report was also issued in September 2009 providing further details for computations

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PART I

Assessment of consistency of treatment effect in MRCTs

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Assessment of Consistency of Treatment Effects in MRCTs

OUTLINE

- Definitions for consistency assessments
- Properties of the proposed definitions – Power for showing consistency
- Other considerations
  - Random Effect Model
  - Binary endpoint
  - Survival endpoint
- Trial example with a continuous endpoint
- Conclusion

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Notations 1/3

- Notations and terminology (continuous and normally distributed endpoint)
  - s = number of regions
  - X_{ij} and Y_{ij} = respectively the control and experimental treatment group endpoint values for the jth patient within region i
  - $X_{ij} \sim N(\mu_{iX},\sigma_i^2)$ and $Y_{ij} \sim N(\mu_{iY},\sigma_i^2)$, i=1,…,s
  - For simplicity of presentation:
    - Equal numbers of patients in each treatment group within a region
    - Variances are equal across groups and regions ($\sigma_1^2 = \ldots = \sigma_s^2 = \sigma^2$)
  - N_i = number of patients per group in region i
  - N = Sum of N_i , i=1,…s

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Notations 2/3

- Notations and terminology (continuous and normally distributed endpoint)
  - Let $\delta_i = \mu_{iY} - \mu_{iX}$ be the true treatment effect within region i (positive value = better outcome)
  - Estimate: $\hat{\delta} = \bar{Y}_i - \bar{X}_i \approx N\left(\delta, \frac{2\sigma^2}{N_i}\right)$
  - Common estimate of the overall treatment effect δ:

$$\hat{\delta} = \frac{\sum_{i=1}^{s} N_i \hat{\delta}}{N} \approx N\left(\delta, \frac{2\sigma^2}{N}\right)$$

  - $f_i = N_i / N$ proportion of patients within region i
  - $u_i = \delta_i / \delta$ = ratio of the treatment effect in region i to the overall effect
  - Then: $\sum_{i=1}^{s} f_i = 1$ and $\sum_{i=1}^{s} f_i u_i = 1$

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Notations 3/3

- The per group overall sample size that achieves 1-β power to detect an overall treatment effect of δ with a significance level α one-sided test is:

$$N = \frac{2\sigma^2 (z_{1-\alpha} + z_{1-\beta})^2}{\delta^2}$$

Definitions for consistency assessments

DEFINITION 1

Achieving in each region a specified proportion π of the observed overall effect:

$$\hat{\delta}_1 > \pi\hat{\delta}, \hat{\delta}_2 > \pi\hat{\delta}, \ldots, and\ \hat{\delta}_s > \pi\hat{\delta}.$$

- **Probability to claim consistency by Definition 1 is:**

$$\Pr\left(Z_i = (1-\pi\ f_i)\hat{\delta}_i - \pi\sum_{j\neq i}^{s} f_j\ \hat{\delta}_j > 0, i=1,\ldots,s \middle| \delta_i\ , i = 1,\ldots,s \right)$$

Definitions for consistency assessments

- **Conditional probability to claim consistency given that there is an overall significant treatment effect by definition 1 is:**

$$\frac{\Pr\left(Z_i > 0, i = 1,\ldots,s;\ Z_{s+1} > z_{1-\alpha}\sigma\sqrt{\frac{2}{N}} \mid \delta, i = 1,\ldots s \right)}{1-\phi\left(z_{1-\alpha} - \frac{\delta}{\sigma\sqrt{2/N}} \right)}$$

$$\left(Z_{s+1} = \sum_{i=1}^{s} f_i \hat{\delta}_i \right)$$

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Definitions for consistency assessments

- **$(Z_1, Z_2,\ldots,Z_{s+1})^T$ is a multivariate normal random vector with mean:**

$$\Delta(\pi) = \delta \begin{pmatrix} u_1 - \pi \\ \mathrm{M} \\ u_s - \pi \\ 1 \end{pmatrix}$$

= 0 if π=1

and covariance matrix:

$$\Sigma(\pi) = 2\sigma^2 \begin{pmatrix} \frac{1}{N}(\pi^2 - 2\pi + \frac{1}{f1}) & \frac{1}{N}(\pi^2 - 2\pi)\ \Lambda & \frac{1}{N}(\pi^2 - 2\pi) & \frac{1}{N}(1-\pi) \\ \frac{1}{N}(\pi^2 - 2\pi) & \frac{1}{N}(\pi^2 - 2\pi + \frac{1}{f2})\ \Lambda & \frac{1}{N}(\pi^2 - 2\pi) & \frac{1}{N}(1-\pi) \\ \mathrm{M} & \mathrm{M} & \mathrm{M} & \mathrm{M} \\ \frac{1}{N}(\pi^2 - 2\pi) & \frac{1}{N}(\pi^2 - 2\pi)\ \mathrm{K} & \frac{1}{N}(\pi^2 - 2\pi + \frac{1}{fs}) & \frac{1}{N}(1-\pi) \\ \frac{1}{N}(1-\pi) & \frac{1}{N}(1-\pi)\ \Lambda & \frac{1}{N}(1-\pi) & \frac{1}{N} \end{pmatrix}$$

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Definitions for consistency assessments

- **Probability and conditional probability for claiming consistency can be calculated by means of usual computations related to multivariate normal distributions**
- **EITHER by Simulations OR by exact numerical integrations**
- **SAS Macros were developed internally**
- **%MVN SAS Macro allows to generate data from a multivariate normal distribution characterized by its mean vector and its covariance matrix**

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Definitions for consistency assessments

- **Method to generate data from a Multivariate Normal Distribution of mean vector Δ and covariance matrix Σ**
- **The method is based on the following:**

1. **Find a lower triangular matrix A such as : $A\,A^T = \Sigma$ (Cholesky decomposition)**
2. **Let $Y = (Y_1, Y_2, \ldots, Y_{s+1})^T$ be a vector whose components are s+1 independent standard normal variables**
3. **Let Z be $Z = \Delta + AY$ (1)**

Z is a Multivariate Normal Distribution of mean vector Δ and covariance matrix Σ

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Definitions for consistency assessments

- For s=3 regions we have to solve $A\,A^T = \Sigma$ with:

$$A = \begin{pmatrix} x_1 & 0 & 0 & 0 \\ x_5 & x_2 & 0 & 0 \\ x_6 & x_7 & x_3 & 0 \\ x_8 & x_9 & x_{10} & x_4 \end{pmatrix} \qquad \Sigma = \begin{pmatrix} \sigma_1^2 & v_1 & v_1 & v_2 \\ v_1 & \sigma_2^2 & v_1 & v_2 \\ v_1 & v_1 & \sigma_3^2 & v_2 \\ v_2 & v_2 & v_2 & \sigma_4^2 \end{pmatrix}$$

- Coefficients x_i can easily be calculated
- Generate first Y then derive Z using formula (1)
- Pr($Z_1>0$, $Z_2>0$, $Z_3>0$, $Z_4>C$) can also be computed using exact integration methods based on vector Y taking advantage of the independence of its components

Definitions for consistency assessments

DEFINITION 2

Observing region effects that exceed a pre-specified effect size:

$$\hat{\delta}_1 > b,\ \hat{\delta}_2 > b, \ldots, and\ \hat{\delta}_s > b\ (b \geq 0).$$

- Potential advantage of definition 2 over definition 1 is that one may still be able to show consistency if the effects of certain regions are reasonable but not exceptional
- Unconditional and conditional probabilities of claiming consistency are calculated in the same way

Definitions for consistency assessments

DEFINITION 3 (the most rigorous approach)

Demonstrating that region effects exceed a proportion of the overall effect using hypothesis testing where the null and alternative hypotheses are:

H_0: $\delta_1 \leq \pi\delta$ or…or $\delta_s \leq \pi\delta$ versus

H_1: $\delta_1 > \pi\delta$ and…and $\delta_s > \pi\delta$

- This is an Intersection-Union test
- Consistency will be claimed **if H_0 is rejected**
- Much more stringent condition than for definition 1 → very small power
- Note: π=0 is equivalent to demonstrate significant treatment effects for all regions with reduced sample sizes (but larger significance level α' could be envisaged)

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Definitions for consistency assessments

DEFINITION 3 (continued)

- Use confidence interval approach to reject H_0

$$Z'_i = \hat{\delta} - \pi\hat{\delta} - z_{1-\alpha'}\sigma\sqrt{\frac{2}{N}\left(\frac{1}{f_i} - 2\pi + \pi^2\right)} > 0, i = 1,\ldots,s$$

- Unconditional and conditional probabilities of rejection are respectively:

$$\Pr\left(Z'_i > 0, i = 1,\ldots,s \mid \delta, i = 1,\ldots s\right)$$

and

$$\frac{\Pr\left(Z'_i > 0, i = 1,\ldots,s; Z_{s+1} > z_{1-\alpha}\sigma\sqrt{\frac{2}{N}} \mid \delta, i = 1,\ldots s\right)}{1 - \phi\left(z_{1-\alpha} - \frac{\delta}{\sigma\sqrt{2/N}}\right)}$$

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Definitions for consistency assessments

DEFINITION 4

Absence of significant treatment-by-region interaction

- The null and alternative hypotheses are:

  H_0: $\delta_1 = \delta_2 = \ldots = \delta_s = \delta$ versus

  H_1: δ_i , i=1,…,s are not all the same
- Consistency claimed **if H_0 not rejected** at a significance level ε (usually ε = 0.1 or even more)
- Statistical validity questionable
- Consistency claimed if :

$$Q = \sum_{i=1}^{s} \frac{(\hat{\delta}_i - \hat{\delta})^2}{2\sigma^2 / N_i} = \frac{\sum_{i=1}^{s} (\hat{\delta}_i - \hat{\delta})^2 N_i}{2\sigma^2} < \chi^2_{s-1}(\varepsilon)$$

- Unconditional and conditional powers are the same

Definitions for consistency assessments

DEFINITION 5

Lack of significant difference for any regions from the overall

- One tests the one-sided individual hypotheses:

  H_0: $\delta_i \geq \delta$ versus H_1: $\delta_i < \delta$, i=1,…,s

- Consistency claimed if none of the H_0's is rejected at a significance level α'
- Statistical validity questionable
- Unconditional and conditional powers are the same
- Allows the detection of the sources of the inconsistency
- Correction for multiplicity issue: α'=ε/s
- Consistency claimed if: $Z_i^* = \hat{\delta}_i - \hat{\delta} - z_{1-\alpha'}\,\sigma\sqrt{\frac{2}{N}\left(\frac{1}{fi} - 1\right)} > 0,\ i = 1,..,s$

Comparisons between the definitions

- Unconditional and conditional probabilities or powers of showing consistency were investigated for the cases of s=3 or 4 regions and different configurations of region sizes and effect sizes
- Only results with s=3 regions are displayed in this presentation
- For illustration purpose, we used the following parameters:
  - α = 0.025, 1-β = 0.8 or 0.9, δ = 0.25 and σ = 1
- The total sample size N is calculated in order to have 1-β power to detect at α = 0.025 level an overall treatment effect of δ = 0.25

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Unconditional and conditional probabilities (%) for claiming consistency

3 Regions, Definitions 1-3

Unconditional and conditional probabilities (%) for claiming consistency based on definitions 1-3 s=3 regions, α=0.025, δ=0.25, σ=1

(f_1, f_2, f_3)	(u_1, u_2, u_3)	Uncond.	Cond.	Uncond.	Cond.	Uncond.	Cond.
	1-β=0.9	Definition 1 π=1/3		Definition 2 b=0.083		Definition 3 π=0, α'=0.3	
(1/3,1/3,1/3)	(1,1,1)	76	81	72	78	76	82
(0.2,0.2,0.6)	(1,1,1)	69	73	66	72	66	72
(1/3,1/3,1/3)	(0.9,1,1.1)	75	80	71	77	75	82
(1/3,1/3,1/3)	(0.6,1.2,1.2)	65	69	62	68	67	73
(0.2,0.2,0.6)	(0.7,0.7,1.2)	49	53	49	53	47	51
(0.2,0.2,0.6)	(1.2,1.1,0.9)	76	80	72	78	73	79
(0.2,0.4,0.4)	(0.8,1.1,1)	68	72	65	71	66	72
(0.1,0.45,0.45)	(1.9,0.9,0.9)	80	85	75	82	79	85

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Unconditional and conditional probabilities (%) for claiming consistency

3 Regions, Definitions 4-5

Probabilities (%) for claiming consistency based on definitions 4 and 5 s=3 regions, α=0.025, δ=0.25, σ=1			
(f_1, f_2, f_3)	(u_1, u_2, u_3)	Uncond. / Cond.	Uncond. / Cond.
1-β=0.9		Definition 4 ε=0.1	Definition 5 α' = 0.1/3
(1/3,1/3,1/3)	(0.25,0.55,2.2)	20	37
(1/3,1/3,1/3)	(0.3,0.3,2.4)	10	27
(1/3,1/3,1/3)	(0.5,0.7,1.8)	51	63
(1/4,1/4,1/2)	(0.3,0.3,1.7)	36	45
(1/4,1/4,1/2)	(0.3,3.1,0.3)	3	15
(1/4,1/4,1/2)	(0.25,0.55,1.6)	47	53
(1/4,1/4,1/2)	(0.25,2.65,0.55)	12	35
(1/4,1/4,1/2)	(0.5,0.7,1.4)	70	72

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Other considerations 1/3

- **Random effect model**
  - Hung (DIA, 2007) : the region effect is considered to be a **random** effect
  - All computations / derivations are provided in the technical report
  - BUT Does it make sense ???
- **Binary endpoint**
  - Apply classical asymptotically normal distributions for differences of rates or relative risk ratios to previous definitions
  - BUT the asymptotic variances may not be the same across all regions
  - This has to be taken into account in calculating the probability of showing consistency

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Other considerations 2/3

- **Survival endpoint 1/2**
  - Proportional hazards model: $\lambda_1(t) = \lambda_0(t)\, e^{\gamma}$ where:
    - $\lambda_1(t)$ and $\lambda_0(t)$ are the hazard functions for active and control
    - e^{γ} is the hazard ratio between treatment and placebo
    - $1- e^{\gamma}$ is the risk reduction
  - Log-rank test statistic $T \sim N(\gamma\sqrt{E}/2, 1)$ where E is the expected total number of events from the two groups combined
  - Asymptotically: $\hat{\gamma} = \frac{2T}{\sqrt{\hat{E}}} \approx N(\gamma, \frac{4}{E})$
  - Overall effect: $\gamma^* = \sum_{i=1}^{s} E_i \gamma / E$

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Other considerations 3/3

- **Survival endpoint 2/2**
  - By the delta method:

$$(1-e^{\hat{\gamma}}) \approx N\left(1-e^{\gamma}, \frac{4}{E_i}(e^{\gamma})^2\right) \quad (1-e^{\hat{\gamma}^*}) \approx N\left(1-e^{\gamma^*}, \frac{4}{E}(e^{\gamma^*})^2\right)$$

  - With:

$$COV(1-e^{\hat{\gamma}}, 1-e^{\hat{\gamma}^*}) = \frac{4}{E} e^{\gamma} e^{\gamma^*}$$

  - Apply the previous method to risk reduction estimates (RRe)

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Trial example 1/2

- Multi-regional trial with 4 regions
- Primary objective: evaluate the effect of a test drug versus placebo on change from baseline in HbA_{1c}
- Unbalanced design 1:2 (1 placebo, 2 test drug) to maximize safety database
- Study overpowered with regard to efficacy to obtain an amount of safety data required for regulatory purposes:

  558 patients (186 placebo, 372 test drug) → >99% power to detect a treatment difference of δ=0.005 with σ=0.013 at α=0.025

Issue:

Determine the minimum required proportion of sample size for a particular region, say Region 1, so that there is an 80% probability of showing consistency.

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Trial example 2/2

Minimum f_1 to have 80% power of showing consistency for Definitions 1-3

	Uncond.	Cond.	Uncond.	Cond.	Uncond.	Cond.
	Def 1 π=1/4		Def 2 b=0.005/4		Def 3 α'=0.4 , π=0	
$f_1 < f_2 = f_3 = f_4$	0.14	0.13	0.23	0.18	0.09	0.08
$f_1 = f_2 < f_3 = f_4$	0.18	0.17	0.24	0.21	0.13	0.13
$f_1 = f_2 = f_3 < f_4$	0.20	0.20	0.24	0.22	0.16	0.16

(All 4 regions are assumed to have the same effect size)

WARNING: if the overall sample size corresponded to 95% overall power a value of f_1 giving 80% unconditional power for showing consistency using Definition 2 may not exist.

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CONCLUSION PART I 1/2

- There are multiple ways to define consistency of treatment effect across regions
- Definitions based on hypothesis testing, i.e. doing an inference about the true effect sizes are more difficult to implement mainly due to lack of power
- In practice, definitions need to be tailored to address the specificity of each trial and/or clinical development
- The main objective of this work was to provide statistical tools to compute unconditional and conditional probabilities of showing consistency of treatment effect across regions

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CONCLUSION PART I 2/2

- It is essential to clarify objectives at design stage to determine upfront the minimum required proportion of sample size for particular region(s)
  - Extensive discussion with HAs is needed to know (minimum) local requirements
- **Key objective**: control adequately the split of sample size by region in a multi-regional trial in order to get a waiver of bridging study for a particular region

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PART II

Sample size considerations for Japanese patients in MRCTs based on MHLW guidance

OUTLINE

- MHLW guidance – Japanese context
- Preserving a fraction of the overall treatment effect in the subset of Japanese patients
- Derivation of sample size formulas for normal, binary and survival endpoints
- Results
- Trial example
- Conclusion

MHLW guidance – Japanese context

- To streamline and expedite new drug development in Japan, the MHLW promotes Japan's participation in multi-regional trials
- With the inclusion of a sufficient number of Japanese patients in these trials, it is possible to assess potential ethnic differences within the trials
- The MHLW guidance provides two methods as examples for deciding on the number of Japanese subjects in a multi-regional trial

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Preserving a fraction of the overall treatment effect in the subset of Japanese patients

- **Method 1**
  - Observed treatment effect D_{all} for the overall population
  - Observed treatment effect D_j for Japanese patients
  - Sample size for Japanese patients in the trial should satisfy:

$$\Pr(D_j / D_{all} > \pi) \geq 1 - \beta' \quad (1)$$

  - Where π is ≥ 0.5 and 1-β' is 0.8 or greater
- **Method 2**
  - A special case of Definition 2 when b=0
  - Not addressed in this presentation

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Derivation of sample size formulas (for a continuous endpoint)

- **Notations:**
  - N_J and N_{NJ} = sample sizes per treatment group in Japanese and non Japanese patients respectively
  - Overall sample size per group $N = N_J + N_{NJ}$
  - δ_J and δ_{NJ} = true treatment effects
  - Overall true treatment effect $\delta = \delta_{all} = (N_J \delta_J + N_{NJ} \delta_{NJ})/N$
  - **$\delta_J = u\, \delta_{NJ}$**
  - Let f_u be the corresponding minimum fraction of Japanese patients which satisfies (1)
  - Sample size per group is calculated as follows:

$$N = \frac{2\sigma^2 (z_{1-\alpha/2} + z_{1-\beta})^2}{\delta^2} \quad (2)$$

Derivation of sample size formulas (for a continuous endpoint)

- **Calculations 1/4**
  - **Since $\Pr(\hat{\delta}_{all} \le 0 \,|\, \delta_{all} = \delta) = \phi(-z_{1-\alpha/2} - z_{1-\beta})$ is very close to 0**
  - **Condition (1) is essentially:**

$$\Pr(\hat{\delta}_J > \pi \hat{\delta}_{all} \,|\, \delta_J, \delta_{NJ}) \ge 1 - \beta' \quad (3)$$

Derivation of sample size formulas (for a continuous endpoint)

- **Calculations 2/4**
  - With $\hat{\theta} = (N - \pi N_J)\hat{\delta}_J - \pi N_{NJ}\hat{\delta}_{NJ} \approx N(\theta, \omega^2)$
    where:
    $$\begin{cases} \theta = (N - \pi N_J)\delta_J - \pi N_{NJ}\delta_{NJ} \\ \omega^2 = 2\sigma^2 N \dfrac{N + (\pi^2 - 2\pi)N_J}{N_J} \end{cases} \quad (4)$$
  - (3) becomes:

$$\Pr(\hat{\theta} > 0 \mid \delta_J, \delta_{NJ}) = \Pr((\hat{\theta} - \theta)/\varpi > -\theta/\varpi \mid \delta_J, \delta_{NJ}) \geq 1 - \beta'$$

$$\Leftrightarrow \frac{(N - \pi N_J)\delta_J - \pi N_{NJ}\delta_{NJ}}{\varpi} \geq z_{1-\beta'} \quad (5)$$

Derivation of sample size formulas (for a continuous endpoint)

- **Calculations 3/4**
  - From (4) and (5), f_u satisfies:

$$\frac{(z_{1-\alpha/2} + z_{1-\beta})\sqrt{f_u}\,(u - \pi - \pi(u-1)f_u)}{(1 + (u-1)f_u)\sqrt{1 + (\pi^2 - 2\pi)f_u}} = z_{1-\beta'} \quad (6)$$

  - For a general u, (6) has no closed-form solution for f_u
  - For given α, β, β',π and u a numerical solution can be derived without much difficulty

Derivation of sample size formulas (for a continuous endpoint)

- **Calculations 4/4**
  - **If u=1 a closed-form solution can be obtained as follows:**

$$f_1 = \frac{z^2_{1-\beta'}}{(z_{1-\alpha/2} + z_{1-\beta})^2 (1-\pi)^2 + z^2_{1-\beta'}(2\pi - \pi^2)} \quad (7)$$

Derivation of sample size formulas (for a continuous endpoint)

- **Having a positive trial and simultaneously satisfy the MHLW requirement**
- **Probability is:**

$$\Pr(\hat{\delta}_J - \pi\hat{\delta}_{all} > 0\,,\ \hat{\delta}_{all} - z_{1-\alpha/2}\sigma/\sqrt{N/2} > 0 \,|\, \delta_J, \delta_{NJ}) \quad (8)$$

- **Correlation between $\hat{\theta} = N(\hat{\delta}_J - \pi\hat{\delta}_{all})$ and $N\hat{\delta}_{all}$ is:**

$$\rho = \frac{(1-\pi)\sqrt{N_J}}{\sqrt{N + (\pi^2 - \pi)N_J}}$$

- **If N_J is replaced by $f_1 N$:** $\rho = \dfrac{z_{1-\beta'}}{z_{1-\alpha/2} + z_{1-\beta}}$

Derivation of sample size formulas (for a continuous endpoint)

- When $\delta_J = \delta_{NJ} = \delta$, Probability (8) becomes:

$$\psi = \Pr\left(Z_1 > -\rho\sqrt{\frac{N}{2}}\frac{\delta}{\sigma}, Z_2 > z_{1-\alpha/2} - \sqrt{\frac{N}{2}}\frac{\delta}{\sigma} \right)$$

  where (Z_1, Z_2) has a bivariate standard normal distribution with correlation ρ

- For any fixed a and b:

$$\psi = \Pr(Z1 > a, Z2 > b) = \int_b^{\infty} \varphi(Z2)\, \phi\left(\frac{\rho\, Z2 - a}{\sqrt{1-\rho^2}} \right) dZ2$$

Derivation of sample size formulas (for a continuous endpoint)

- Ψ is an increasing function of ρ
- Minimum is achieved when ρ=0
- No closed-form solution for the minimum number of Japanese patients such that (8) is greater than a pre-specified value
- Ψ can be calculated by numerical integrations

Results 1/2

π = 0.5

Values of $f_{0.9}$, f_1, $f_{1.1}$, ρ and ψ (two-sided α=0.05)								
π	**1-β**	**1-β'**	**$f_{0.9}$**	**f_1**	**$f_{1.1}$**	**(1-β)(1-β')**	**ρ**	**ψ**
0.5	0.90	0.80	0.290	0.224	0.174	0.720	0.260	0.735
0.5	0.95	0.80	0.248	0.187	0.143	0.760	0.233	0.768
0.5	0.90	0.85	0.383	0.313	0.253	0.765	0.320	0.781
0.5	0.95	0.85	0.334	0.265	0.209	0.808	0.288	0.816
.0.5	0.90	0.90	0.494	0.426	0.361	0.810	0.395	0.826
0.5	0.95	0.90	0.437	0.367	0.303	0.855	0.356	0.864

Results 2/2

π = 0.7

Values of $f_{0.9}$, f_1, $f_{1.1}$, ρ and ψ (two-sided α=0.05)								
π	**1-β**	**1-β'**	**$f_{0.9}$**	**f_1**	**$f_{1.1}$**	**(1-β)(1-β')**	**ρ**	**ψ**
0.7	0.90	0.80	0.541	0.445	0.349	0.720	0.260	0.735
0.7	0.95	0.80	0.494	0.390	0.294	0.760	0.233	0.768
0.7	0.90	0.85	0.635	0.559	0.474	0.765	0.320	0.781
0.7	0.95	0.85	0.587	0.500	0.408	0.808	0.288	0.816
.0.7	0.90	0.90	0.726	0.673	0.612	0.810	0.395	0.826
0.7	0.95	0.90	0.681	0.616	0.543	0.855	0.356	0.864

Trial example 1/2

- Same example of a normal endpoint as for Part I
  - Endpoint: change from baseline in HbA_{1c}
  - One-sided α=0.025
  - Target effect = difference of 0.005 versus placebo
  - Standard deviation = 0.013
  - Overall power of 99% (to satisfy regulatory safety database requirements)
  - 186 patients in placebo group, 372 patients in test drug group

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Trial example 2/2

- Sample size for Japanese patients

π	1-β'	f_1	N_{IJ} based on f_1	
			Placebo (N=186)	Treatment (N=372)
0.5	0.80	0.138	26	51
0.5	0.85	0.199	37	74
0.5	0.90	0.282	52	105
0.6	0.80	0.200	37	75
0.6	0.85	0.280	52	104
0.6	0.90	0.380	71	141
0.7	0.80	0.308	57	115
0.7	0.85	0.408	76	152
0.7	0.90	0.522	97	194

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Binary and survival endpoints

- All formulas can be extended to **binary** endpoints by replacing $2\sigma^2$ by $p_1(1-p_1) + p_0(1-p_0)$ where p_1 and p_0 are the true event rates for treatment and placebo respectively
- Adaptations to a **survival** endpoint are addressed in the technical report

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Conclusion – Part II 1/2

- This presentation addressed Method 1 for showing consistency as suggested in the MHLW guidance
- If the true treatment effects for Japanese patients and the other patients are the same, closed-form solutions are available
- Otherwise numerical approaches are needed
- The method can be (in theory) expanded to any other region (e.g. Europe, USA,…)
- However, both the general results and the example in HbA_{1C} showed that the minimum required proportion of Japanese patients is growing quickly with the fraction π of the overall (observed) treatment effect one wants to preserve in Japanese patients
- This proportion may be significantly inflated when the treatment effect for Japanese patients is smaller than the one for other patients

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Conclusion – Part II 2/2

- Example in HbA_{1C} may not be representative as the study was clearly overpowered
- Also the proposed method is based on observed treatment effects and NOT on a true statistical inference about the true treatment effect
  - Questionable from a pure statistical point of view BUT better than nothing !
  - Is it acceptable by HAs ?
  - By construction the study will generally be underpowered to make a statistical inference in particular region(s)
- It is not obvious that preserving e.g. 50% or even 70% of the (observed) treatment effect as compared to other patients could be accepted by HAs : this is still a significant loss of efficiency which could trigger bridging studies

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KEY MESSAGES TO TAKE HOME

- The current trend of global new drug development strategy is to have a multi-regional trial approach
- Demonstration of consistency of treatment effects across regions and ethnical groups is a key requirement
- Objective is that patients can access effective and safe drugs simultaneously worldwide

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KEY MESSAGES TO TAKE HOME

- The MLHW guidance suggests possible approaches for showing consistency
- **BUT this is a first step:** Regulators need to achieve a global consensus about common approaches / requirements
- This presentation provides a statistical framework to address the consistency issue at design stage
- The proposed approach is flexible: a variety of adaptations can easily be implemented

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