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

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


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

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
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.

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.
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.

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 the 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 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
PART I

Assessment of consistency of treatment effect 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
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
- \( X_{ij} \sim N(\mu_{iX}, \sigma_{iX}^2) \) and \( Y_{ij} \sim N(\mu_{iY}, \sigma_{iY}^2) \), \( i=1,\ldots,s \)
- 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
- \( N = \text{Sum of } N_i, i=1,\ldots,s \)

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: \( \hat{\delta} = \bar{Y} - \bar{X}_i \approx N \left[ \delta, \frac{2\sigma^2}{N_i} \right] \)
- Common estimate of the overall treatment effect \( \delta \):
  \[
  \delta = \frac{\sum_{i=1}^{s} N_i \hat{\delta}}{N} = N \left[ \delta, \frac{2\sigma^2}{N} \right] 
  \]
- \( f_i = N_i / N \) 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 \( \sum_{i=1}^{s} f_i u_i = 1 \)
Notations 3/3

The per group overall sample size that achieves $1-\beta$ power to detect an overall treatment effect of $\delta$ with a significance level $\alpha$ 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 $\pi$ of the observed overall effect:

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

Probability to claim consistency by Definition 1 is:

$$\Pr\left(Z_i = (1-\pi f_i)\hat{\delta}_i - \pi \sum_{j=1}^s f_j \hat{\delta}_j > 0, i=1,...,s \mid \delta_i, i = 1,...,s\right)$$
Definitions for consistency assessments

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

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

\[
= 1 - \phi\left(z_{1 - \sigma} - \frac{\delta}{\sigma\sqrt{2/N}}\right)
\]

\[
(Z_s + 1 = \sum_{i=1}^{s} f_i \hat{\delta})
\]

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

\[
\Delta(\pi) = \begin{pmatrix} u_i - \pi \\ M \\ u_i - \pi \end{pmatrix}
\]

and covariance matrix:

\[
\Sigma(\pi) = 2\sigma^2
\begin{pmatrix}
\frac{1}{N}(\pi^2 - 2\pi + \frac{1}{M}) & \frac{1}{N}(\pi^2 - 2\pi) & \frac{1}{N}(\pi^2 - 2\pi) \\
\frac{1}{N}(\pi^2 - 2\pi) & \frac{1}{N}(\pi^2 - 2\pi + \frac{1}{M}) & \frac{1}{N}(\pi^2 - 2\pi) \\
\frac{1}{N}(\pi^2 - 2\pi) & \frac{1}{N}(\pi^2 - 2\pi) & \frac{1}{N}(\pi^2 - 2\pi + \frac{1}{M})
\end{pmatrix}
\]
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 $\Delta$ and covariance matrix $\Sigma$

- The method is based on the following:

  1. Find a lower triangular matrix $A$ such as: $A \cdot A^T = \Sigma$ (Cholesky decomposition)

  2. Let $Y = (Y_1, Y_2, ..., Y_{s+1})^T$ 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 $\Delta$ and covariance matrix $\Sigma$
Definitions for consistency assessments

For \( s=3 \) regions we have to solve \( A A^T = \Sigma \) with:

\[
A = \begin{pmatrix}
    x_1 & 0 & 0 & 0 \\
    x_2 & x_3 & 0 & 0 \\
    x_4 & x_5 & x_6 & 0 \\
    x_7 & x_8 & x_9 & x_{10}
\end{pmatrix}, \quad \Sigma = \begin{pmatrix}
    \sigma_1^2 & \sigma_1 \sigma_2 & \sigma_1 \sigma_3 & \sigma_1 \\
    \sigma_2 \sigma_1 & \sigma_2^2 & \sigma_2 \sigma_3 & \sigma_2 \\
    \sigma_3 \sigma_1 & \sigma_3 \sigma_2 & \sigma_3^2 & \sigma_3 \\
    \sigma_1 & \sigma_2 & \sigma_3 & \sigma^2
\end{pmatrix}
\]

- 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:

\[
\hat{\delta}_1 > b, \hat{\delta}_2 > b, \ldots, \hat{\delta}_s > b \quad (b \geq 0).
\]

- 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:

\[ H_0: \delta_1 \leq \pi \delta \text{ or...or } \delta_s \leq \pi \delta \text{ versus} \]

\[ H_1: \delta_1 > \pi \delta \text{ and...and } \delta_s > \pi \delta \]

This is an Intersection-Union test

Consistency will be claimed if \( H_0 \) is rejected

Much more stringent condition than for definition 1 \( \rightarrow \) very small power

Note: \( \pi = 0 \) is equivalent to demonstrate significant treatment effects for all regions with reduced sample sizes (but larger significance level \( \alpha' \) could be envisaged)

Definitions for consistency assessments

DEFINITION 3 (continued)

Use confidence interval approach to reject \( H_0 \)

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

Unconditional and conditional probabilities of rejection are respectively:

\[ \Pr(Z' > 0, i = 1,\ldots,s \mid \delta, i = 1,\ldots,s) \]

\[ \text{and} \quad \Pr\left(Z' > 0, i = 1,\ldots,s; Z_{\cdot\cdot} > z_{1-\alpha} \sigma \sqrt{\frac{2}{N}} \mid \delta, i = 1,\ldots,s \right) \]

\[ 1 - \phi \left( z_{1-\alpha} - \frac{\delta}{\sigma \sqrt{2/ N}} \right) \]
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

  \( H_1: \delta_i, i=1,\ldots,s \) are not all the same
- Consistency claimed if \( H_0 \) not rejected at a significance level \( \epsilon \) (usually \( \epsilon = 0.1 \) or even more)
- Statistical validity questionable
- Consistency claimed if:
  \[
  Q = \sum_{i=1}^{s} (\hat{\delta}_i - \hat{\delta})^2 \frac{2}{2\sigma^2 / N_i} = \frac{1}{2\sigma^2} \left( \sum_{i=1}^{s} (\hat{\delta}_i - \hat{\delta})^2 N_i \right) < \chi^2_{s-1}(\epsilon)
  \]
- Unconditional and conditional powers are the same

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 \( H_1: \delta_i < \delta, i=1,\ldots,s \)
- Consistency claimed if none of the \( H_0 \)'s is rejected at a significance level \( \alpha' \)
- Statistical validity questionable
- Unconditional and conditional powers are the same
- Allows the detection of the sources of the inconsistency
- Correction for multiplicity issue: \( \alpha' = \epsilon/s \)
- Consistency claimed if:
  \[
  Z_{\hat{\delta}_i} = \hat{\delta}_i - \hat{\delta} - z_{1-\alpha'} \sqrt{\frac{2}{N (1 - \frac{1}{s})}} > 0, i=1,\ldots,s
  \]
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:
  - \( \alpha = 0.025, \ 1-\beta = 0.8 \) or \( 0.9, \ \delta = 0.25 \) and \( \sigma = 1 \)

- The total sample size \( N \) is calculated in order to have \( 1-\beta \) power to detect at \( \alpha = 0.025 \) level an overall treatment effect of \( \delta = 0.25 \).

Unconditional and conditional probabilities or powers of claiming consistency

<table>
<thead>
<tr>
<th>( (f_1, f_2, f_3) )</th>
<th>( (u_1, u_2, u_3) )</th>
<th>Uncond.</th>
<th>Cond.</th>
<th>Uncond.</th>
<th>Cond.</th>
<th>Uncond.</th>
<th>Cond.</th>
</tr>
</thead>
<tbody>
<tr>
<td>( (1/3,1/3,1/3) )</td>
<td>( (1,1,1) )</td>
<td>76</td>
<td>81</td>
<td>72</td>
<td>78</td>
<td>76</td>
<td>82</td>
</tr>
<tr>
<td>( (0.2,0.2,0.6) )</td>
<td>( (1,1,1) )</td>
<td>69</td>
<td>73</td>
<td>66</td>
<td>72</td>
<td>66</td>
<td>72</td>
</tr>
<tr>
<td>( (1/3,1/3,1/3) )</td>
<td>( (0.9,1,1.1) )</td>
<td>75</td>
<td>80</td>
<td>71</td>
<td>77</td>
<td>75</td>
<td>82</td>
</tr>
<tr>
<td>( (1/3,1/3,1/3) )</td>
<td>( (0.6,1.2,1.2) )</td>
<td>65</td>
<td>69</td>
<td>62</td>
<td>68</td>
<td>67</td>
<td>73</td>
</tr>
<tr>
<td>( (0.2,0.2,0.6) )</td>
<td>( (0.7,0.7,1.2) )</td>
<td>49</td>
<td>53</td>
<td>49</td>
<td>53</td>
<td>47</td>
<td>51</td>
</tr>
<tr>
<td>( (0.2,0.2,0.6) )</td>
<td>( (1.2,1.0,1.0) )</td>
<td>76</td>
<td>80</td>
<td>72</td>
<td>78</td>
<td>73</td>
<td>79</td>
</tr>
<tr>
<td>( (0.2,0.4,0.4) )</td>
<td>( (0.8,1.1,1.1) )</td>
<td>68</td>
<td>72</td>
<td>65</td>
<td>71</td>
<td>66</td>
<td>72</td>
</tr>
<tr>
<td>( (0.1,0.45,0.45) )</td>
<td>( (1.9,0.9,0.9) )</td>
<td>80</td>
<td>85</td>
<td>75</td>
<td>82</td>
<td>79</td>
<td>85</td>
</tr>
</tbody>
</table>
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, \( \alpha = 0.025 \), \( \delta = 0.25 \), \( \sigma = 1 \)

<table>
<thead>
<tr>
<th>((f_1, f_2, f_3))</th>
<th>((u_1, u_2, u_3))</th>
<th>Uncond. / Cond.</th>
<th>Uncond. / Cond.</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1/3,1/3,1/3)</td>
<td>((0.25,0.55,2.2))</td>
<td>20</td>
<td>37</td>
</tr>
<tr>
<td>(1/3,1/3,1/3)</td>
<td>((0.3,0.3,2.4))</td>
<td>10</td>
<td>27</td>
</tr>
<tr>
<td>(1/3,1/3,1/3)</td>
<td>((0.5,0.7,1.8))</td>
<td>51</td>
<td>63</td>
</tr>
<tr>
<td>(1/4,1/4,1/2)</td>
<td>((0.3,0.3,1.7))</td>
<td>36</td>
<td>45</td>
</tr>
<tr>
<td>(1/4,1/4,1/2)</td>
<td>((0.3,0.3,0.3))</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>(1/4,1/4,1/2)</td>
<td>((0.25,0.55,1.6))</td>
<td>47</td>
<td>53</td>
</tr>
<tr>
<td>(1/4,1/4,1/2)</td>
<td>((0.25,2.65,0.55))</td>
<td>12</td>
<td>35</td>
</tr>
<tr>
<td>(1/4,1/4,1/2)</td>
<td>((0.5,0.7,1.4))</td>
<td>70</td>
<td>27</td>
</tr>
</tbody>
</table>

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
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
  - $e^\gamma$ 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: $\hat{\gamma} = \frac{2T}{\sqrt{E}} \approx N(\gamma, \frac{4}{E})$
- Overall effect: $\gamma^* = \sum_{i=1}^{s} \frac{E_i \gamma / E}{E}$

Other considerations 3/3

**Survival endpoint 2/2**

- By the delta method:
  $$1 - e^{\hat{\gamma}} = N\left(1 - e^\gamma, \frac{4}{E_i} (e^\gamma)^2\right)$$
  $$1 - e^{\hat{\gamma}^*} = N\left(1 - e^\gamma, \frac{4}{E} (e^\gamma)^2\right)$$
- 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)
Multi-regional trial with 4 regions

Primary objective: evaluate the effect of a test drug versus placebo on change from baseline in HbA₁c

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) \(\rightarrow\) >99% power to detect a treatment difference of \(\delta=0.005\) with \(\sigma=0.013\) at \(\alpha=0.025\)

**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.

<table>
<thead>
<tr>
<th>Minimum (f) to have 80% power of showing consistency for Definitions 1-3</th>
<th>Uncond.</th>
<th>Cond.</th>
<th>Uncond.</th>
<th>Cond.</th>
<th>Uncond.</th>
<th>Cond.</th>
</tr>
</thead>
<tbody>
<tr>
<td>(f_1 \times f_2 = f_3 \times f_4)</td>
<td>0.10</td>
<td>0.13</td>
<td>0.13</td>
<td>0.23</td>
<td>0.18</td>
<td>0.09</td>
</tr>
<tr>
<td>(f_1 = f_1 \times f_1 \times f_1)</td>
<td>0.18</td>
<td>0.17</td>
<td>0.24</td>
<td>0.21</td>
<td>0.13</td>
<td>0.13</td>
</tr>
<tr>
<td>(f_1 \times f_1 \times f_1)</td>
<td>0.20</td>
<td>0.20</td>
<td>0.24</td>
<td>0.22</td>
<td>0.16</td>
<td>0.16</td>
</tr>
</tbody>
</table>

(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 \(f\), giving 80% unconditional power for showing consistency using Definition 2 may not exist.
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

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
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.

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

  Where $\pi$ is $\geq 0.5$ and $1 - \beta'$ is 0.8 or greater

Method 2

- A special case of Definition 2 when $b=0$
- Not addressed in this presentation
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 \( N = N_j + N_{NJ} \)
- \( \delta_j \) and \( \delta_{NJ} \) = 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 \( f_j \) be the corresponding minimum fraction of Japanese patients which satisfies (1)
- Sample size per group is calculated as follows:

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

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

\[
\Pr(\hat{\delta}_t > \pi\hat{\delta}_{all} | \hat{\delta}_t, \hat{\delta}_{all}) \geq 1 - \beta' \quad (3)
\]
Derivation of sample size formulas
(for a continuous endpoint)

Calculations 2/4

With \( \hat{\theta} = (N - \pi N_J) \hat{\delta}_j - \pi N N_J \hat{\delta}_N \approx N(\theta, \omega^2) \)

where:
\[
\begin{align*}
\theta &= (N - \pi N_J) \delta_j - \pi N N_J \delta_N \\
\omega^2 &= 2\sigma^2 N \frac{N + (\pi^2 - 2\pi)N_J}{N_J}
\end{align*}
\] (4)

(3) becomes:
\[
\Pr(\hat{\theta} > 0 | \delta_j, \delta_N) = \Pr((\hat{\theta} - \theta) / \sigma > -\theta / \sigma | \delta_j, \delta_N) \geq 1 - \beta'
\]
\[
\iff \frac{(N - \pi N_J) \delta_j - \pi N N_J \delta_N}{\sigma} \geq z_1 - \beta' \quad (5)
\]

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 \( \alpha, \beta, \beta', \pi \) 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:

\[
f_1 = \frac{z_{1-\beta}^2}{(z_{1-\alpha/2} + z_{1-\beta})^2 (1-\pi)^2 + z_{1-\beta}^2 (2\pi - \pi^2)}
\]  

(7)

Having a positive trial and simultaneously satisfy the MHLW requirement

Probability is:

\[
\Pr(\hat{\delta} - \pi\hat{\delta}_{all} > 0, \hat{\delta}_{all} - z_{1-\alpha/2} / \sigma / \sqrt{N/2} > 0 \mid \delta_i, \delta_{all})
\]

(8)

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

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

If \( N_j \) is replaced by \( f_jN \):

\[
\rho = \frac{z_{1-\beta}}{z_{1-\alpha/2} + z_{1-\beta}}
\]
Derivation of sample size formulas (for a continuous endpoint)

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

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

where $(Z_1, Z_2)$ has a bivariate standard normal distribution with correlation $\rho$

- For any fixed $a$ and $b$:

$$\psi = \Pr (Z_1 > a, Z_2 > b) = \int_b^\infty \phi(Z_2) \phi \left( \frac{\rho Z_2 - a}{\sqrt{1-\rho^2}} \right) dZ_2$$

- $\Psi$ is an increasing function of $\rho$
- Minimum is achieved when $\rho = 0$
- No closed-form solution for the minimum number of Japanese patients such that (8) is greater than a pre-specified value
- $\Psi$ can be calculated by numerical integrations
### Results 1/2

**π = 0.5**

Values of $f_{0.9}$, $f_1$, $f_{1.1}$, $\rho$ and $\psi$ (two-sided $\alpha = 0.05$)

<table>
<thead>
<tr>
<th>π</th>
<th>1-β</th>
<th>1-β'</th>
<th>$f_{0.9}$</th>
<th>$f_1$</th>
<th>$f_{1.1}$</th>
<th>$(1-\beta)(1-\beta')$</th>
<th>$\rho$</th>
<th>$\psi$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>0.90</td>
<td>0.80</td>
<td>0.290</td>
<td>0.224</td>
<td>0.174</td>
<td>0.720</td>
<td>0.260</td>
<td>0.735</td>
</tr>
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<td>0.80</td>
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<td>0.187</td>
<td>0.143</td>
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<td>0.233</td>
<td>0.768</td>
</tr>
<tr>
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<td>0.85</td>
<td>0.383</td>
<td>0.313</td>
<td>0.253</td>
<td>0.765</td>
<td>0.320</td>
<td>0.781</td>
</tr>
<tr>
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<td>0.85</td>
<td>0.334</td>
<td>0.265</td>
<td>0.209</td>
<td>0.808</td>
<td>0.288</td>
<td>0.816</td>
</tr>
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<td>0.90</td>
<td>0.494</td>
<td>0.426</td>
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<td>0.855</td>
<td>0.356</td>
<td>0.864</td>
</tr>
</tbody>
</table>

### Results 2/2

**π = 0.7**

Values of $f_{0.9}$, $f_1$, $f_{1.1}$, $\rho$ and $\psi$ (two-sided $\alpha = 0.05$)

<table>
<thead>
<tr>
<th>π</th>
<th>1-β</th>
<th>1-β'</th>
<th>$f_{0.9}$</th>
<th>$f_1$</th>
<th>$f_{1.1}$</th>
<th>$(1-\beta)(1-\beta')$</th>
<th>$\rho$</th>
<th>$\psi$</th>
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</thead>
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<tr>
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<td>0.720</td>
<td>0.260</td>
<td>0.735</td>
</tr>
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<td>0.7</td>
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<td>0.80</td>
<td>0.494</td>
<td>0.390</td>
<td>0.294</td>
<td>0.760</td>
<td>0.233</td>
<td>0.768</td>
</tr>
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<td>0.85</td>
<td>0.635</td>
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<td>0.474</td>
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<td>0.320</td>
<td>0.781</td>
</tr>
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<td>0.543</td>
<td>0.855</td>
<td>0.356</td>
<td>0.864</td>
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</tbody>
</table>
Trial example 1/2

Same example of a normal endpoint as for Part I

- Endpoint: change from baseline in HbA\textsubscript{1c}
- One-sided $\alpha=0.025$
- 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

Trial example 2/2

Sample size for Japanese patients

<table>
<thead>
<tr>
<th>$\pi$</th>
<th>1-$\beta'$</th>
<th>$f_1$</th>
<th>$N_{IJ}$ based on $f_1$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo (N=186)</td>
</tr>
<tr>
<td>0.5</td>
<td>0.80</td>
<td>0.138</td>
<td>26</td>
</tr>
<tr>
<td>0.5</td>
<td>0.85</td>
<td>0.199</td>
<td>37</td>
</tr>
<tr>
<td>0.5</td>
<td>0.90</td>
<td>0.282</td>
<td>52</td>
</tr>
<tr>
<td>0.6</td>
<td>0.80</td>
<td>0.200</td>
<td>37</td>
</tr>
<tr>
<td>0.6</td>
<td>0.85</td>
<td>0.280</td>
<td>52</td>
</tr>
<tr>
<td>0.6</td>
<td>0.90</td>
<td>0.380</td>
<td>71</td>
</tr>
<tr>
<td>0.7</td>
<td>0.80</td>
<td>0.308</td>
<td>57</td>
</tr>
<tr>
<td>0.7</td>
<td>0.85</td>
<td>0.408</td>
<td>76</td>
</tr>
<tr>
<td>0.7</td>
<td>0.90</td>
<td>0.522</td>
<td>97</td>
</tr>
</tbody>
</table>
**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 HbA1c showed that the minimum required proportion of Japanese patients is growing quickly with the fraction $\pi$ 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.
Example in HbA\textsubscript{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**
**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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**References**