EVALUATION OF IMPOSING AN ADDITIONAL REQUIREMENT AND SAMPLE SIZE PLANNING FOR MULTI-REGIONAL CLINICAL TRIALS

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Multi-Regional Clinical Trials (MRCT)

- Definition
  - Multi-regional clinical trials (MRCT) is the trial conducted simultaneously in multiple regions under the same trial protocol in principle.
- Objectives of MRCT
  - Show global efficacy
  - Get regional approval
    - Show consistency in treatment effect between global results and each region.

Consistency Requirements in MRCT

- Two types of proposed consistency requirement:
  - Type 1: Evaluate if the "estimated" treatment effect of region *i* preserves some fixed proportion of the "estimated" overall treatment effect, i.e.

$$D_i > \pi_i \, D \qquad (1)$$

  - Type 2: Test if the treatment effect based on the samples from region *i* is statistically significant at level α_i, i.e.

$$Z_{i0} = \frac{D_i}{std(D_i)} > z_{1-\alpha_i} \qquad (2)$$

- We propose: unified consistency requirement
  - Test if the "true" treatment effect of region i preserves some fixed proportion of the "true" overall treatment effect at significance level α_i.

Unified Consistency Requirement

- The unified consistency requirement is as follows:

$$Z_i = \frac{D_i - \pi_i D}{std(D_i - \pi_i D)} > z_{1-\alpha_i} \qquad (3)$$

where Z_i is the test statistic for the following hypothesis test:

$$H_0: \mu_i \leq \pi_i \mu \ \text{ versus } \ H_a: \mu_i > \pi_i \mu$$

- The proposed consistency requirement (3) generalizes the two consistency requirements (1) & (2)
  - When $\alpha_i = 0.5$, i.e. $z_{1-\alpha_i} = 0$, (3) will be reduced to (1);
  - When $\pi_i = 0$, (3) will be reduced to (2).
- Two parameters (π_i, α_i) are included in the proposed unified consistency requirement, making it more feasible in practice.

Power, Assurance Probability and Success Rate

- Success of entire MRCT: overall power

$$Power = P_{\mu}(Z > z_{1-\alpha})$$

- Success of each region given overall efficacy: assurance probability
  - Definition: the probability of the region *i* satisfying the consistency requirement given the overall efficacy.

$$AP_i = P_{\mu}(Z_i > z_{1-\alpha_i} | \, Z > z_{1-\alpha})$$

- Success of each region: success rate

$$SR_i = P_{\mu}(Z > z_{1-\alpha}, Z_i > z_{1-\alpha_i})$$
$$= \text{Power} * AP_i$$

Determination of Parameters (π_i, α_i)

- Question: what are the reasonable values of (π_i, α_i)?
  - Consistency requirement: $D_i > \pi_i D, \pi_i = 0.5$.
  - Under ideal settings: $\mu_i = \mu, \sigma_i = \sigma, f_i = \frac{1}{s}$.
  - Denote N the sample size to achieve 80% overall power at one-sided significance level 0.025; N^* the sample size needed to achieve certain level of assurance probability for all regions.

- More samples needed
  - Include more regions in an MRCT
  - Anticipate larger assurance probability for each region

$\rho = N^*/N$					
AP	s=2	s=3	s=4	s=5	s=6
0.8	1	1	1	1.35	1.81
0.85	1	1	1.66	2.29	2.87
0.9	1	1.77	2.70	3.56	4.40

Determination of Parameters (π_i, α_i)

- To avoid the need of consuming huge samples to preserve certain *AP*, we determine the values of (π_i, α_i) by considering
  - Number of regions (s)
  - Practical sample size increase (ρ)
- Recommendations of combinations of (π_i, α_i) for 2 to 6 regions:

(π_i, α_i)				
s=2	s=3	s=4	s=5	s=6
(0,0.075)	(0,0.15)	(0.0,0.225)	(0,0.275)	(0,0.325)
(0.1,0.10)	(0.1,0.20)	(0.1,0.275)	(0.1,0.325)	(0.1,0.375)
(0.3,0.175)	(0.3,0.30)	(0.3,0.375)	(0.3,0.45)	(0.325,0.5)
(0.5,0.30)	(0.5,0.425)	(0.5,0.5)	(0.4,0.5)	
(0.7,0.5)	(0.575,0.5)			

  - These pairs make each region have approximate 80% assurance probability with the sample size of 80% power under the ideal settings.
  - The assurance probability will be around 85% and 90% for each region with 1.5-fold and 2-fold the sample size of 80% power, respectively.

Optimal Designs for MRCT

- Sample size planning for an MRCT is uncommonly based on the ideal settings, e.g. differences in treatment effect, disease prevalence, commercial viability, etc.
- The sample size planned based on the traditional method may not be large enough to guarantee certain assurance probability for all regions of interest.
- Optimal designs
  - Take all differences among regions into consideration when designing MRCT
  - Appropriately allocate samples to each region and increase total sample size if necessary to ensure certain overall power and assurance probability of regions of interest.
- We propose two optimal designs
  - Minimal total sample size design (MTSS)
  - Maximal utility design (MU)

Minimal Total Sample Size Design

- Determine the minimal sample size and the corresponding sample size proportion for each region to achieve both the desired overall power and desired assurance probabilities of all regions of interest, i.e.

  Minimize: *N* (with the corresponding $f_i, i = 1, \dots, s$)

  Subject to:

$$Power \geq 1 - \beta$$
$$AP_i \geq 1 - \beta_i, i = 1, \dots, j$$

  where $1 - \beta$ is the desired overall power; $1 - \beta_i$ is the desired assurance probability for region i; $j \leq s$ is the number of regions of interest.

Maximal Utility Design

- Find the optimal sample size allocation, which maximizes the global utility of the regions of interest on the premise of guaranteeing the desired overall power with the fixed total sample size, i.e.

  Maximize: $U = \sum_{i=1}^{j} M_i AP_i$ (with the corresponding $f_i, i = 1, \ldots, s$)

  Subject to:

$$Power \geq 1 - \beta$$
$$N = N_0$$

  where M_i is the utility weight of region i which could be related to number of patients or commercial viability of this region and $\sum_{i=1}^{j} M_i = 1$; $1 - \beta$ is the desired overall power; N_0 is the fixed total sample size; $j \leq s$ is the number of regions of interest.

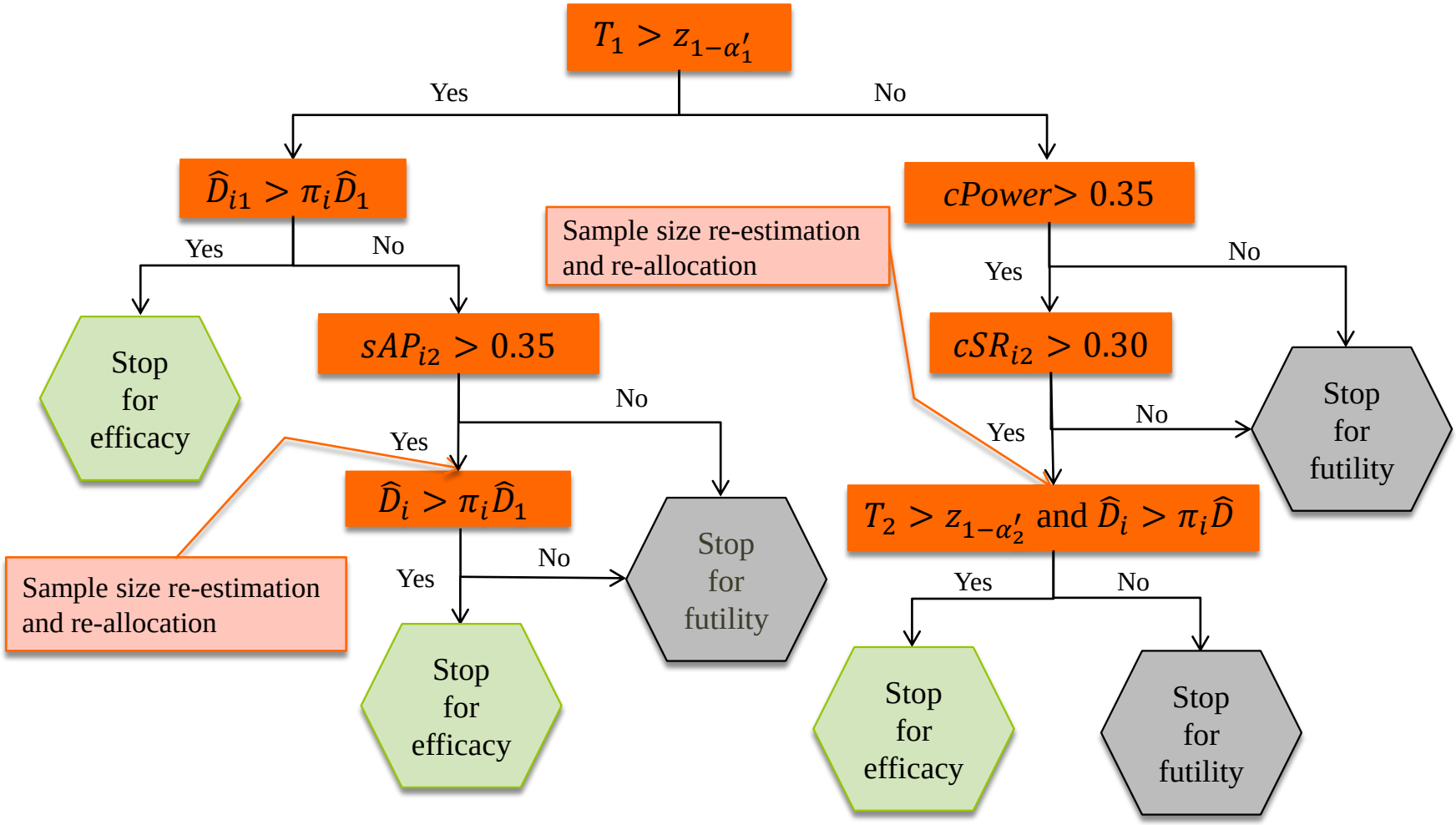
Elements to Consider when Designing MRCT

- Treatment effect for each region
  - Estimate from historical trials or early stage data
- MTSS: Desired assurance probability for each region
- MU: Utility weight for each region
  - Determine by considering patients' benefit, commercial viability, etc.
- Consistency requirement
  - Mainly determined by local regulatory agencies, but still negotiable in some cases.
  - MRCT-extension trial may be required, the final decision of regional approval is based on samples from both MRCT and MRCT- extension trial.
- Regions of interest in an MRCT
- ……

Adaptive Design for MRCT

- In terms of MRCT for a common disease, conducting with a fixed design may be sufficient; the proposed optimal designs can handle this scenario.
- However, if no historical information is available for a disease, an adaptive design may be preferable by applying different re-allocation ratios to different regions and possibly by increasing sample size after an interim analysis of the ongoing trial.
- We propose: region-level adaptive design for MRCT
  - The entire MRCT and each individual region are allowed to be stopped at interim for efficacy or futility, or to continue to the next stage with sample size re-estimation and/or re-allocation based on the observed data.
  - Consistency requirement: $D_i > \pi_i D$

Flow Chart of Adaptive Design (Two-stage)



Adaptive Strategies (Two-stage AD)

- Step 1: Initial sample size planning
  - Optimal designs
- Step 2: Decision making and sample size adaptation at interim
  - **Scenario 1:** $T_1 > z_{1-\alpha_1'}$ and $\widehat{D}_{i1} > \pi_i \widehat{D}_1$; claim regional efficacy for all regions
  - **Scenario 2:** $T_1 > z_{1-\alpha_1'}$, $\widehat{D}_{i1} > \pi_i \widehat{D}_1, i = 1, \dots, j$, but $\widehat{D}_{i1} < \pi_i \widehat{D}_1, i = j+1, \dots, s$; claim regional efficacy for regions 1 to *j*, stop regions *j*+1 to *s* for futility or enroll more samples to ensure certain sAP_{i2}.
  - **Scenario 3:** $T_1 < z_{1-\alpha_1'}$, *cPower*< 0.35; stop the entire MRCT for futility
  - **Scenario 4:** $T_1 < z_{1-\alpha_1'}$, *cPower*> 0.35; stop region *i* if $cSR_{i2} < 0.30$, conduct sample size re-estimation and re-allocation by using MTSS and/or MU design.

MTSS Design

Minimize: $N_2^* (< N_{\max} - N_1)\ (f_{i2}^*, i = 1, \dots s')$

Suject to:

$$cPower \geq 1 - \beta_2$$

$$cAP_i \geq 1 - \beta_{i2}, i = 1, \dots, s'$$

MU Design

Maximize: $cU_2 = \sum_{i=1}^{s'} M_{i2} cAP_{i2}\ (f_{i2}^*, i = 1, \dots s')$

Suject to:

$$cPower \geq 1 - \beta_2$$

$$N_2^* = N_{\max} - N_1$$

- Step 3: Final decision
  - Claim regional efficacy as long as overall result is significant $T_i > z_{1-\alpha_i'}, i = 1,2$ and the consistency requirement is satisfied $\widehat{D}_i > \pi_i \widehat{D}, i = 1, \dots, s$.

Summary

- Many benefits for conducting MRCT
  - Reduce total cost, save time, benefit more patients, no “drug lag” issue, etc.
- It also presents many challenges. We propose some methodologies to provide solutions to some of these challenges.
  - Each region can specify its own parameters of (π_i, α_i) in the proposed unified consistency requirement in consideration of safety, sample size limitation and other specific reasons.
  - The optimal sample size allocation designs give a solution to the sample size planning, which can guarantee certain overall power and probabilities of satisfying the consistency requirement for all regions of interest.
  - The proposed region-level adaptive design makes MRCT more efficient by applying sample size re-estimation and re-allocation at interim.

Thank you!