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Data Science Round Table

症例数再設計のP3試験への適用事例

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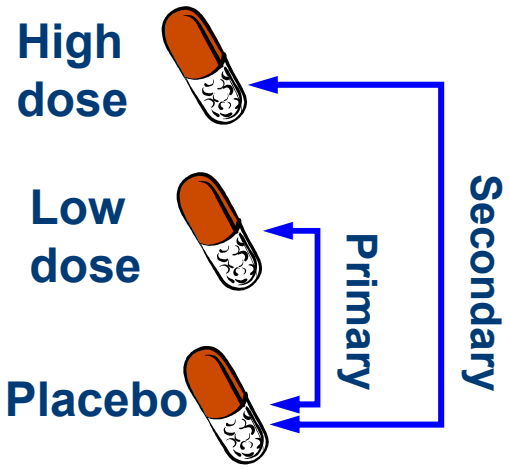
Contents

- A Real Example of Un-Blinded SSR
  - Statistical Consideration
  - Operational Consideration
  - Regulatory Consideration

Background -1

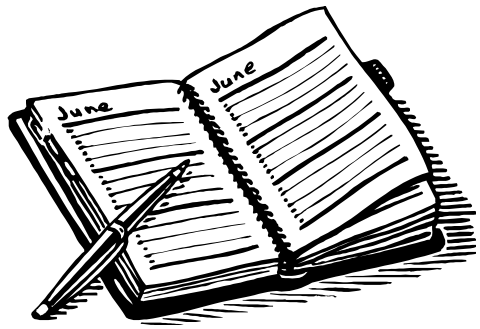
- **Indication**
  - **Peripheral Neuropathic Pain**
- **Drug**
  - **Therapeutic agent for Pain**



- **Study Primary Objective**
  - **Assess superiority of the efficacy of low dose compared to placebo**
- **Study Design**
  - **Randomized, double-blind, parallel group study**
  - **13-week treatment period**

Background -2

- **Randomization ratio**
  - Placebo: Low dose: high dose = 3:3:1
- **Region**
  - Japan
- **Primary efficacy endpoint**
  - Change from baseline in weekly mean pain score
  - Based on “Pain Diary”



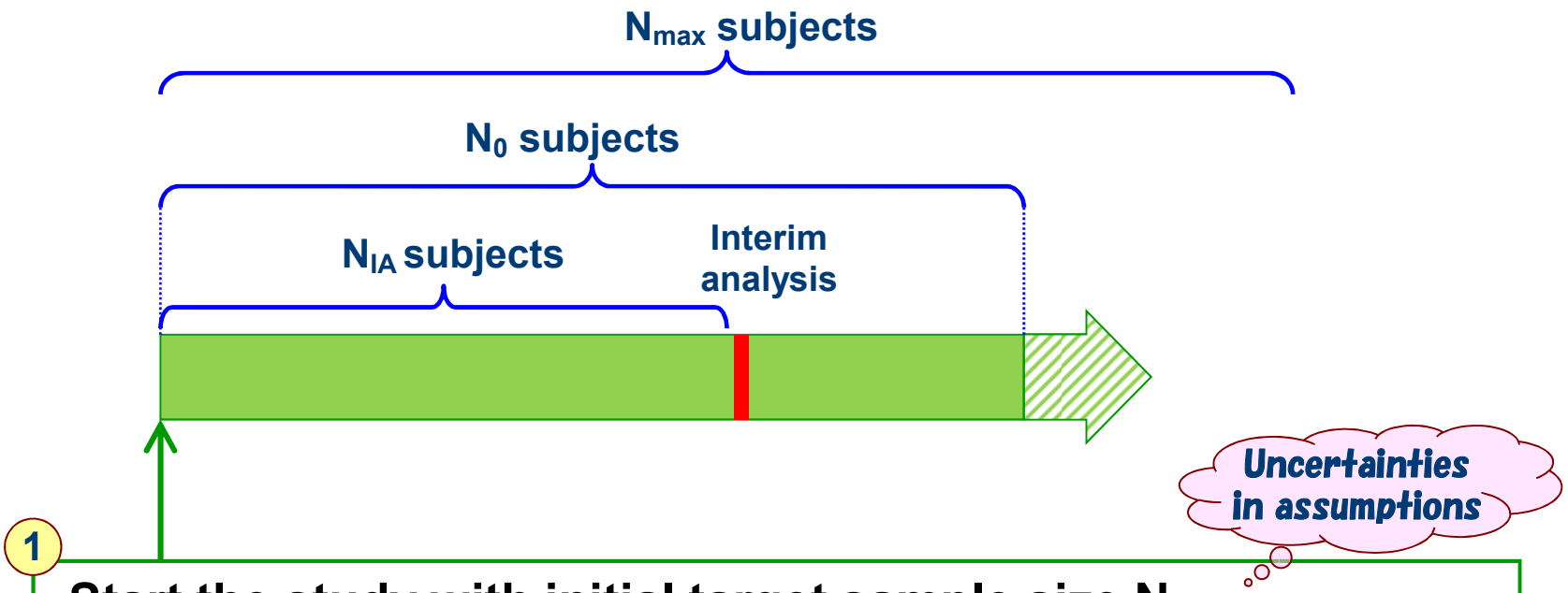
Study design considerations

- **Past experience**
  - No experience in the similar study design for the same pain model, Neuropathic pain associated with diabetic peripheral neuropathy (DPN), in Japan regardless of the drug
  - Experience in this drug in EU and US

- **Challenge**
  - There were uncertainties on the treatment difference and variability in the primary variable in Japanese patients.
    - Japanese patients could have different responses from Westerners due to differences in ethnicity and medical practice in the primary disease (i.e., diabetes mellitus).
    - There was limited information about pain intensity in Japanese DPN patients while reduction in the pain score was affected by the initial (baseline) severity.

- **Consider reassessing treatment difference and variability using the interim data to improve their precision of estimation**

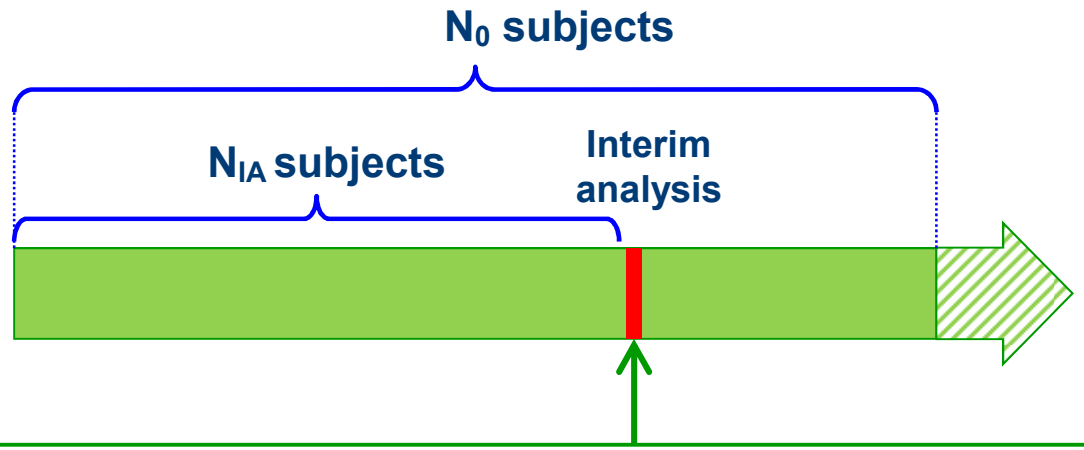
Unblinded SSR: Basic concept -1



1

- Start the study with initial target sample size N_0
- Plan for interim analysis (IA) at N_{IA} subjects
- Be prepared for the maximum allowable sample size (N_{max})
- Clarify the "decision rule" to be used at IA

Unblinded SSR: Basic concept -2

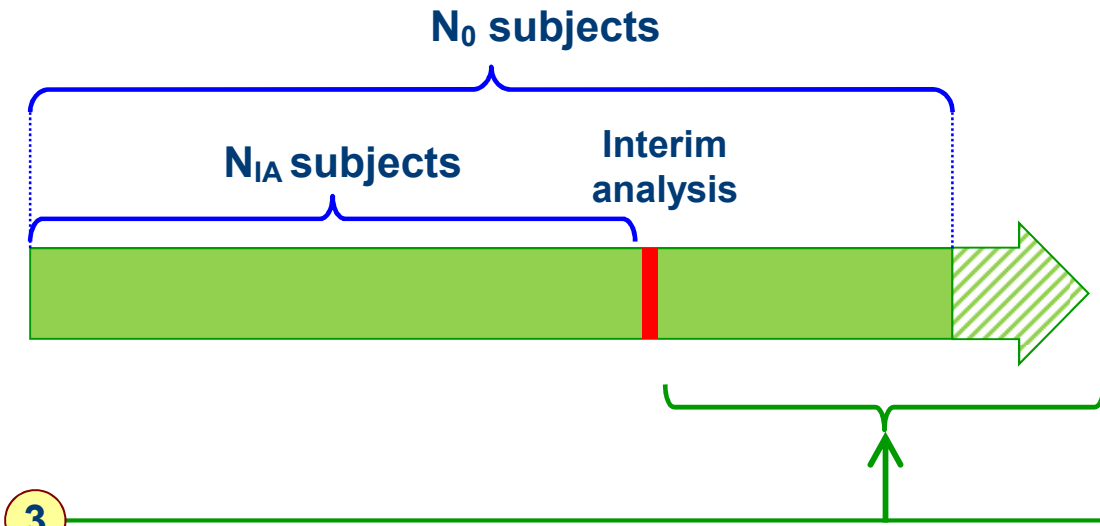


2

- **Estimate treatment difference and variability using interim data**
- **Make a decision based on the "decision rule" using the new treatment difference and variability estimates**

- **Can reduce the level of uncertainty from the planning stage.**

Unblinded SSR: Basic concept -3



3

- Conduct the post-IA part of the study following the decision at IA. Typical decisions:
  - Stay with initial sample size
  - Increase sample size (up to a maximum)
  - Stop the trial for futility

Statistical -1

Basic framework

- **Early efficacy stop – No**
- **Futility stop – Yes**
- **Decrease sample size – No**
- **Maximum sample size – Yes**

Details of decision criteria at IA

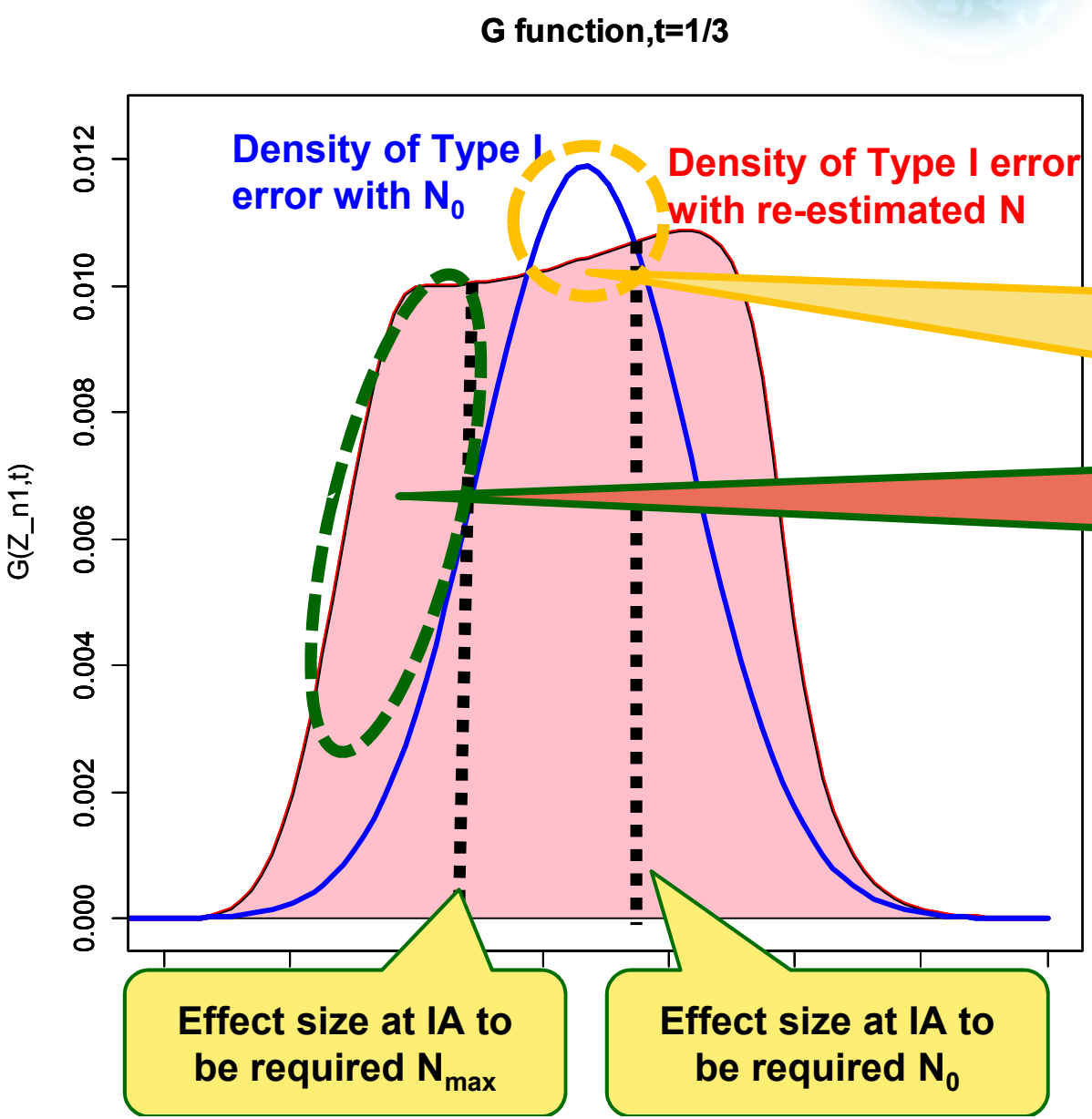
- Based on "conditional power"
- Power
  - ***Probability*** **(**"success" at end of study | when drug is truly effective**)**
- Conditional power (CP)
  - ***Probability*** **(**"success" at end of study | given the IA result when drug is truly effective**)**
  - CP is higher if IA result is "good"
  - CP is lower if IA result is "bad"

Statistical -2

- Details of decision criteria at IA
  - Below procedure does not inflate Type I error (Chen et al. 2004)
    - Note: Decisions 1 and 3 lead to the same action
    - Decisions 2 and 4 are important in avoiding Type I error inflation
    - The Type I error inflation was also checked by Monte-Carlo simulation
  - "Cut points" for CP were determined by assessing operating characteristics for various scenarios.

CP for initial target N_0	Decision
$0.9 \leq CP$	Decision1: Continue to initial target N_0
$0.5 < CP < 0.9$	Decision2: Increase sample size so that CP is 0.9
$0.2 \leq CP \leq 0.5$	Decision3: Continue to initial target N_0
$CP < 0.2$	Decision4: Stop study for futility

Statistical -3



Point1：Type I error will decrease if sample size increase to more than original sample size because true difference is zero

Point2：Type I error will inflate if maximum sample size close to infinity

Point 1 is key statistical technique in sample size re-estimation

Statistical -4

- Initial sample size (N_0)
  - Based on “most likely” estimate using Western reference studies
  - 90% power for primary comparison (Low dose vs. placebo)
- Maximum total sample size (N_{max})
  - Minimum clinically meaningful treatment difference
    - N_{max}=1.5 x N_0の場合，計画時のエフェクトサイズの0.82（√1/1.5）倍を仮定していることとなる。
    - N_{max}=2 x N_0の場合，計画時のエフェクトサイズの0.71（√1/2）倍を仮定していることとなる。
  - Resource restriction (time, cost, etc.)
- Timing of IA
  - Should not be too early → Too little data accumulated
  - Should not be too late → No time to take actions effectively
  - For this study ½ N_0 was selected

Operational -1

- **The interim analysis was conducted at the independent statistical data analysis center (ISDAC), which was operated by a CRO**
  - The internal clinical programmer provided the codes to the ISDAC
- **The dissemination plan was pre-specified:**
  - Number of patients to increase was only notified to the study statistician and reported to specific project members
  - The information was cascaded on a need-to-know basis but who knows the information should be reported to the statistician
- **It was not allowed to report the information to investigators**

Operational -2

- Actual enrolment
  - Enrollment of original number of subjects had been almost completed when the IA results was provided
  - Therefore, stopping rule for futility did not work
    - Decided that the stopping rule was removed before IA conducting

Regulatory -1

- **PMDA**
  - Un-Blinded SSR was accepted
  - A view mentioned in Ando, et al. (2010)*
    - "…, regardless of whether they are blinded or unblinded, variables for interim data collection should be minimal and just sufficient to determine the sample size adjustment."

    *As noted in the article, the views expressed are based on independent work and do not necessarily represent the views of the PMDA

Regulatory -2

- **PMDA: After J-NDA**
  - Explained implementation structure of IA (e.g. IA analysis, randomization schedule transfer, database) and information management of IA results
  - Investigated difference/similarity in baseline characteristics and efficacy results among the IA data, data after IA and final data
  - Our information management of IA
    - For sites, did not inform IA timing and IA results
    - For internal limited study team members, informed only the decision that final sample size was not changed

Summary

- Determine the decision rule of SSR
  - A statistician can provide operating characteristics of each decision rule
  - The decision rule cannot be made without contribution of all team members, especially, CR, SM, Regulatory
- Need to obtain deep understanding of IA with investigators and site staffs
  - No inform regarding IA including progression status of enrollment
- Pre-define IA procedure including information management and follow the IA procedure

Reference

- Chen YH, DeMets DL and Lan K K.(2004). Increasing the sample size when the unblinded interim results is promising. *Statistics in Medicine*, 23:1023–1038.