Adaptive Design for CNS Trials

# Regulatory Issues Related to Use of Adaptive Design in Japan

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- No official support or endorsement by the PMDA is intended or should be inferred.

# Outline

- Introduction
- Experience and discussion in Japan
  - Background of issues in Japan
  - Adaptive design cases in PMDA
  - Discussion in consultation meetings
- Global clinical trials and adaptive design
- Ongoing and future tasks in Japan
- Summary

# Introduction

- Adaptive design
  - allows modification to aspects of the clinical trial based on interim analysis results without undermining the validity and integrity of the trial.
  - plans modification prospectively.
- Why adaptive design?
  - To have a higher probability of success in drug development.

# Introduction

- Issues in adaptive design
  - Statistical issues
  - Operational issues (error/bias)
  - Adaptation in confirmatory trial

# Background of issues in Japan

- Until recently, we had less experience of interim analysis (group sequential design).
  - Except in oncology drug development
- On the other hand, global drug development and active participation in global clinical trials are encouraged.
- It is highly likely that we participate in global trials with adaptive design.

# Adaptive design cases in PMDA

- No approved case with adaptive design
  - At least one case under review
- Many cases in clinical trial consultation meetings

# Adaptive design cases in PMDA

- Cases in clinical trial consultation meetings
  - Design types
    - Sample size re-estimation
    - Adaptive dose-finding
    - Adaptive seamless Phase II/III
  - Disease areas
    - Oncology
    - Orphan disease
    - CNS
  - Region
    - Global/multi-regional trials
    - Japanese trials

# Adaptive design cases in PMDA

- Relationship between design types and disease areas
  - Sample size re-estimation in oncology drug area
    - Recognized as modifications of group sequential trials
  - Adaptive dose-finding in CNS area
    - Because of difficulties in dose finding by traditional dose-response study design

# Discussion in consultation Meetings

- Common discussion points
- Discussion points by design type
  - Sample size re-estimation
  - Adaptive dose-finding
  - Adaptive seamless Phase II/III

# Common discussion points

- Appropriateness of using adaptive design
  - Disease area
    - Number of patients
    - Difficulty of conducting clinical trials
    - Feature of the clinical evaluation
  - Alternative design
    - Traditional design
    - Necessity of another trial to obtain prior information

# Common discussion points

- Appropriateness of using adaptive design
  - Objective of the trial in clinical data package (clinical development program)
    - Sufficiency of the information from adaptive design
    - Sufficiency of the information from clinical data package

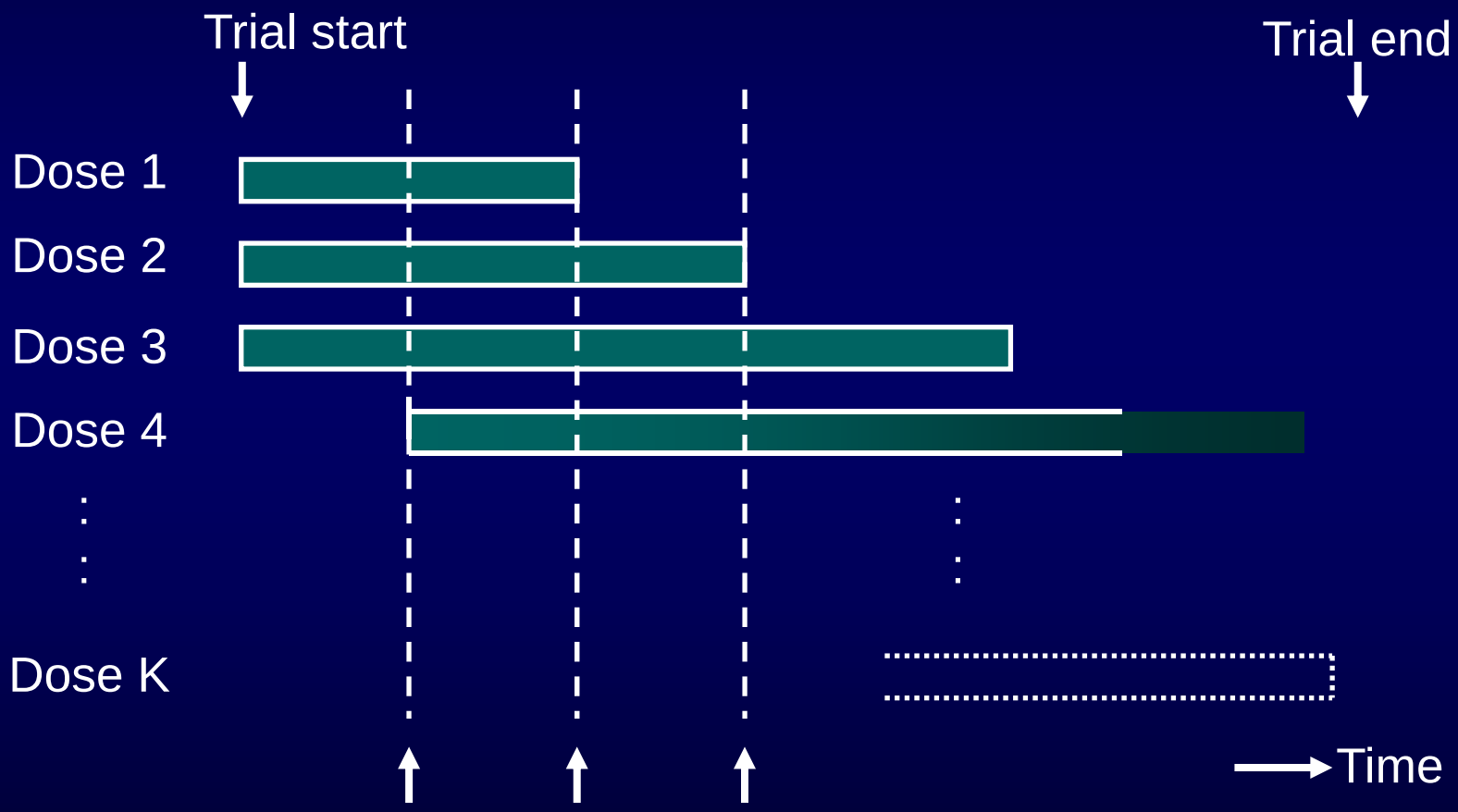
# Discussion points by design type

- Sample size re-estimation
  - Design feature
    - Re-estimate sample size based on interim data (effect size, or deviation only)
    - Blinded or unblinded
  - Discussion
    - Necessity/appropriateness of re-estimation
    - How much data will be opened in interim analysis
    - Independence of staffs who can access analyzed interim data

# Discussion points by design type

- Adaptive dose-finding
  - Background
    - Traditional designs, such as parallel group dose response trial with three or four doses, have limitations
  - Design feature
    - Start with a few arms of dose
    - Add or drop arms or change subject allocation several times based on pre-specified criteria
    - In early stage of drug development

# Discussion points by design type




Interim analysis and adaptive patients allocation

# Adaptive dose-finding may be useful?

- Adaptive dose-finding
  - Discussion
    - Possibility of operational errors with actively conducted interim analysis
    - Sufficiency of dose-response information for subjects in one region (discussed later)

# Discussion points by design type

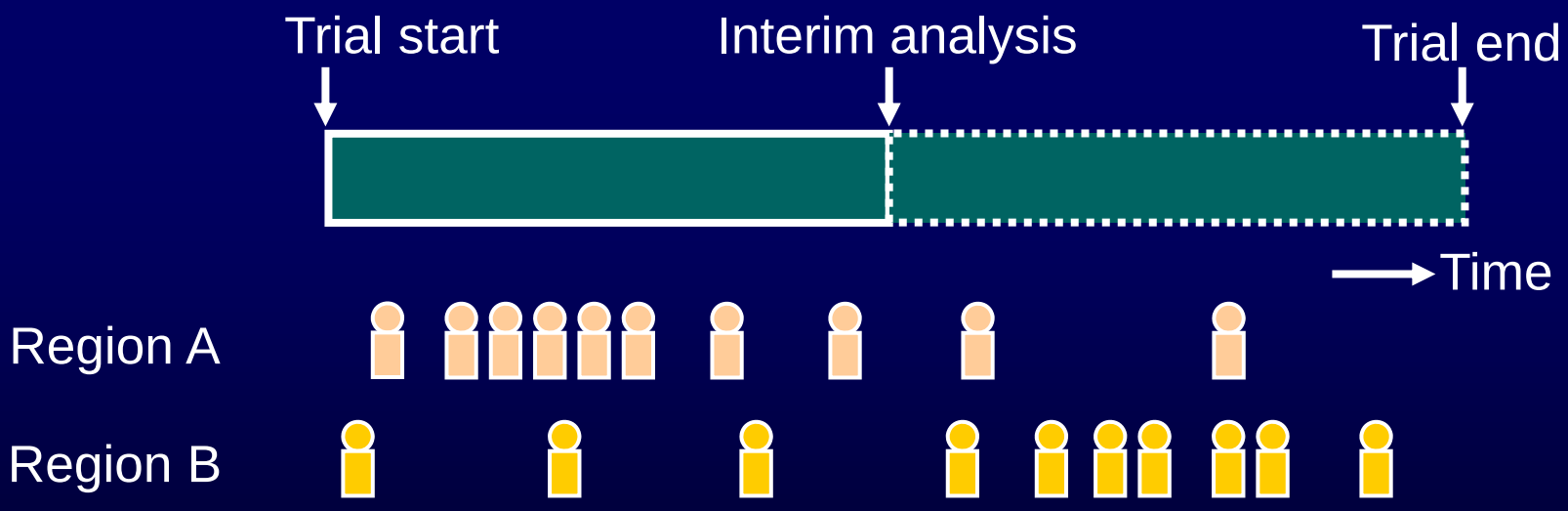
- Adaptive seamless Phase II/III
  - Design feature
    - Combination of dose selection part and confirming part
    - In late stage of drug development
  - Discussion
    - Uncertainty of dose-response relationship
    - Appropriateness of selected doses for dose-selection part
    - Decreasing of dose-response information compared to traditional PII trials
    - Flexible nature vs. confirmatory setting

# Global clinical trials

- For global clinical trials, patients are included from many regions in the world.
- Ethnic difference in drug efficacy and safety may be concern in some disease areas.
  - Intrinsic and extrinsic ethnic factors
- How much data from one region contribute to an interim analysis?
  - Composition of patients from regions vary before and after adaptation?

# Adaptive design in global trials

- Patients recruitment speed of all regions should be considered.



# Issues in global adaptive trials

- Global adaptive dose-finding
  - Sufficiency of dose-response and recommended dose information for all regions
- Global adaptive seamless Phase II/III
  - Appropriateness of selected dose for confirming part for all regions

# Ongoing tasks

- Better understanding of adaptive design
  - Operational consideration
  - Necessary review materials
    - Clinical study report with all statistical analysis results
    - Minutes of data monitoring committee (DMC) meeting
    - Reports of the simulations conducted before adaptive clinical trial

# Future tasks

- Lessons learned from successful cases
- Lessons learned from failure cases
  - Trial failed to accomplish a purpose because of…
    - lack of efficacy?
    - trial design (adaptive design)?

# Summary

- Our goal is to provide
  - more effective and safer drug faster
  - with sufficient information of efficacy and safety.
- We can choose the best design to reach our goal.
  - Adaptive design is an option.
  - Conducting adaptive design clinical trials is not our goal.

# Summary

- Adaptive design could be useful choice in some situations.
- We should consider appropriateness of using of adaptive design.
  - Disease area
  - Alternative design
  - Objective of the trial in clinical data package
- We need more discussion on adaptive design with industry and achademia.

# Thank you for your attention

- Information
  - PMDA Homepage
    - http://www.pmda.go.jp/english/index.html
  - PMDA Drug Information
    - http://www.info.pmda.go.jp/