

Regulatory Experience of Adaptive Designs in Well-Controlled Clinical Trials

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Acknowledgments

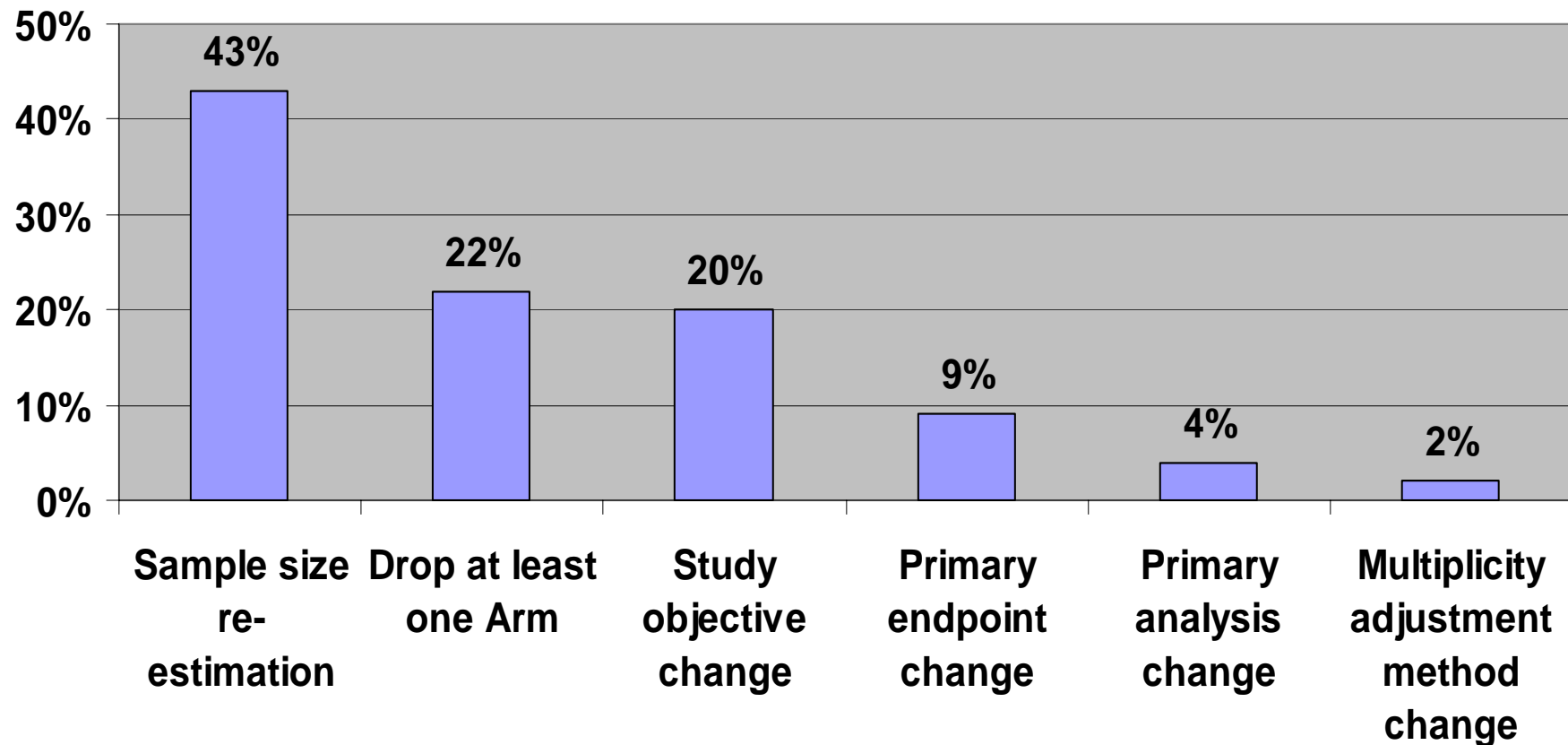
Members of the statistical review teams and clinical review teams across all statistical divisions and medical divisions in CDER, U.S. FDA that work with Office of Biostatistics on the adaptation strategy or adaptive design through IND/NDA submissions

Earlier experience on Design
Elements considered for
Adaptation that impact
statistical analysis, statistical
inferences and results
interpretation

Protocol Amendment(s)

A summary of practice as of Sept. 2002 CDER, FDA; 46 study cases

% Submission by Types of Design Modifications



Wang, Hung, O'Neill, 2005 Proceedings of JSM Biopharmaceutical Section

SWang - PhRMA/FDA 11.14.2006

More Recent Adaptive Designs

Adaptive Seamless phase II/III Design

- **Adaptive:** Use of interim observed data results (blinded or unblinded) for adaptation, where adaptive rules are pre-specified
- **Seamless:** no additional dialogue with regulatory agency after phase II and before phase III
- **Phase II/III:** Accumulated data from phase II & phase III are used for formal statistical inference on primary efficacy endpoint & possibly key secondary endpoint

More Recent Adaptive Designs

Adapt Genomic Subpopulation or Enrichment

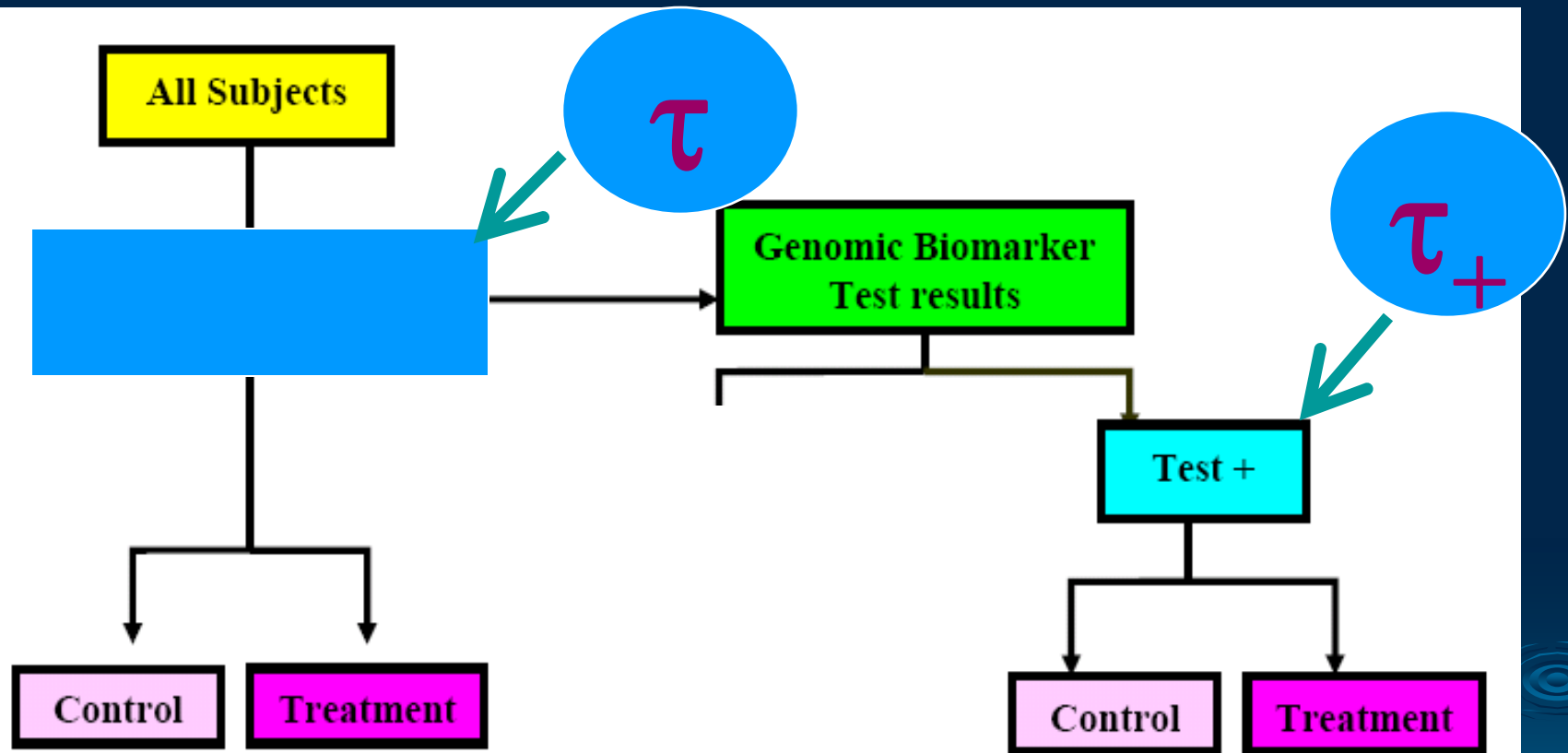


Figure. Use of Genomic Biomarker in Two-Arm Pharmacogenomics Clinical Trial

* Wang, Hung (2005, JSM Biopharmaceutical Proceedings)

* Simon, Wang (2006, The Pharmacogenomics Journal)

Several terms used in ASD Proposals

learn / confirm

Phase IIB / Phase III

Stage 1 / Stage 2

Phase IIA / Phase IIB

Early Aspect / Later Aspect

Part 1 (2-stages) / Part 2

Whatever term is used, the purpose is to consider combining learn/confirm data such that it is a one-trial scenario

What issues the CDER review team raise with ASD proposal - Example 1

Sponsor proposal: a two-stage *ASD* up to 2-year of treatment to evaluate the safety and efficacy of new treatment

Adaptive elements:

- Incorporate the possibility of selecting any 2 out of 4 endpoints
- Reduce the treatment duration based on the outcome of an interim analysis

Current review comments

- 🔹 **Select any 2 out of 4 endpoints:** Given the purported mechanism of action of TRT, two efficacy endpoints may potentially provide best information about therapeutic potential of TRT in the intended patient population
- 🔹 **Reduce treatment duration:** No proposal on multiplicity adjustments on interim analysis, on multiple endpoints, on choice of treatment durations to address the overall type I error control. Hence, the proposed design for adapting the treatment duration based on the outcome of an interim analysis is considered exploratory adaptation.
- 🔹 **The sponsor agreed that adaptive design features for selecting endpoints in this trial would not be applicable. The sponsor plans to use the results based on the interim data of the study to prepare the planning of their phase III program**

What issues the CDER review team raise with ASD proposal - Example2

Proposal: **Open-label**, prospective, multicenter, 5-arm ASD

- Primary efficacy: event occurrence at 6-months
- Rationale
 - **Phase II**: Confirm safety, initial efficacy and optimum dose for the phase 3 study;
 - Dose selection is to be performed within active arms only
 - **Phase III**: Confirm efficacy of selected optimum dose

Review Comments on Design adequacy as an RCT

💧 Design

- Multiplicity issues
- Double-Blind consideration
- Alternative Phase III designs
 - Stand-alone trial; Competing doses trial

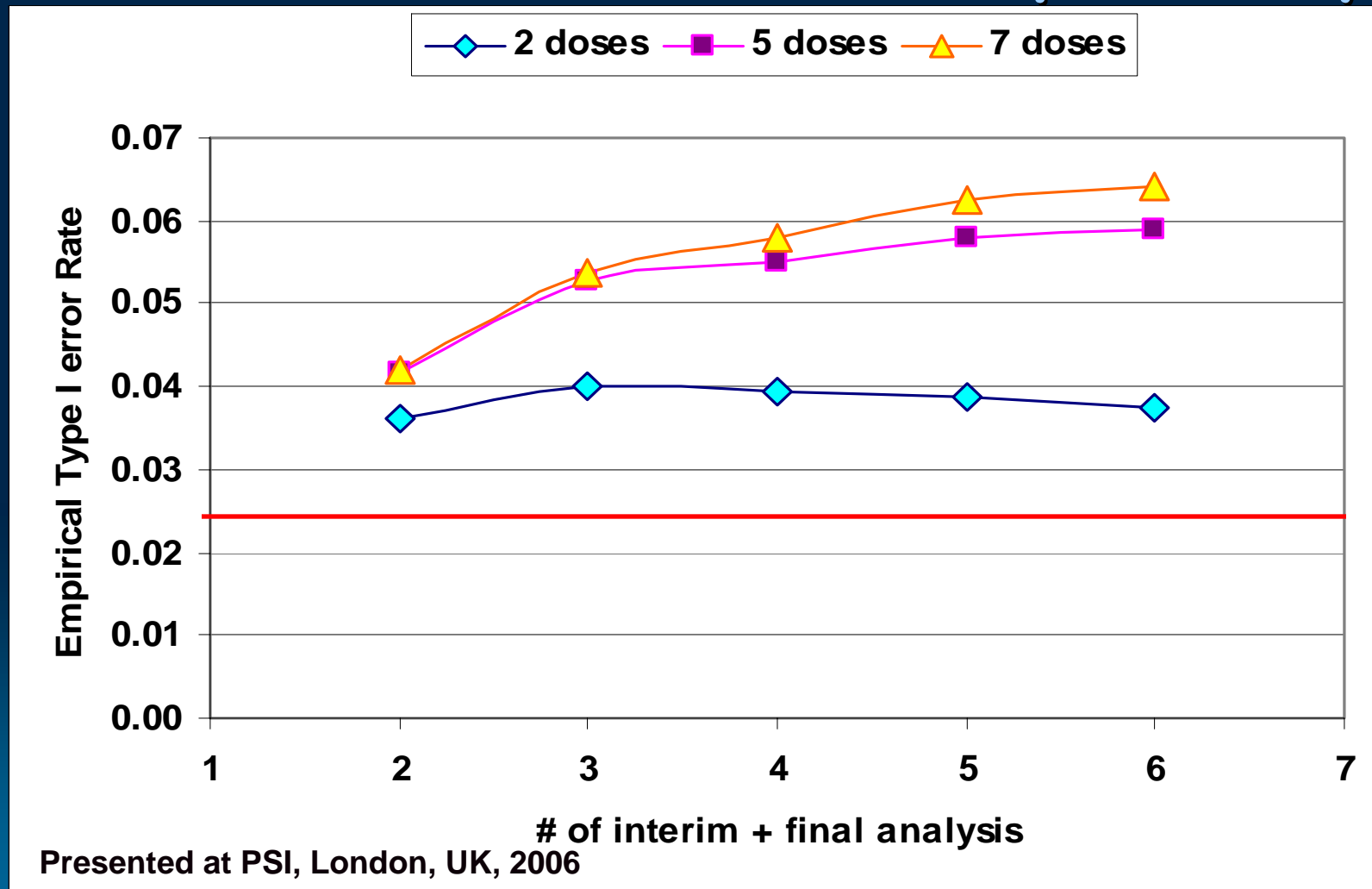
💧 Endpoints

- Clinical endpoints - improved function (e.g. walking distance), event-related (e.g. fewer re-interventions or limb amputations) endpoints, or some composite of these

💧 Simulation studies

- Consider suggested efficacy endpoints

Select among TRT dose groups by imposing $Z_{\max} - Z_j \geq D$ for all j but max, $D=1$, based on outcome endpoint only



Summary of Adaptive Strategy or Adaptive Design Experiences

AD: Single design parameter adaptation

Resize the study: many cases, most benign?
drop ineffective/toxic active dose, depend on objective
change primary endpoint, caution

ASD with at least one design parameter

Select at least one active dose arms (possible resize)
Select primary endpoints (may resize)
Select treatment duration (may resize)
Modify study population, then resize the study
Select primary endpoint, treatment duration
Select treatment duration, trial duration, and resize

ASD within early phases

AD in early phase: dose-escalation, dose-response

Perceived benefits, concerns, information value

Enhance “efficiency” of drug development:

- **Can total number of patients be reduced?**
 - exploratory adaptation in Ph II; confirmatory adaptation in Ph III
 - sample size increase only when necessary
 - dropping an ineffective or toxic arm
 - while adapt these parameters as the experiments move forward, cannot ignore the principles and rationales of AD
- **Can duration of drug development be reduced?**
 - White space b/t Ph II & Ph III shortened by combining planning of both phases & meet regulator before Ph II: lose think time?
 - require resources and time for performing simulation studies that simulate adaptive scenarios

Are these perceived benefits practical?

Potential Impact to Late Stage Attrition Rate

- ◆ Flexibility in planning making it seamless
- ◆ Requires even more careful planning in phase II as scenario planning to increase the chance of success in the combination Ph II/III trial
- ◆ Multiplicity in 2-stage: global H_0 & final H_0
- ◆ Can planning with less prior data within trial w/o other info actually be improved - is this logical?
- ◆ Addition of more prior data external to the ASD trial (cannot skip early exploratory learning) may aid in better (scenario) planning, though less prior data within trial - help reduce late stage attrition

Principles for Adaptive Design

Adhere to Scientific and Statistical Rigor that

- Is prospectively planned
- Has valid statistical approaches on modification of design elements that have α -control (ICH E-9)
- Has valid point estimate and CI estimates
- Utility of drawing strength from external trials, but, not too much
- Careful use of “learning phase” in “confirming” phase
- Has SOP/infrastructure/firewalls on adaptive process monitoring – bias issue & trial integrity
- Has SOP/logistics on adaptive design decision
- Includes documentation of actual monitoring process, extent of compliance, potential impact on study results