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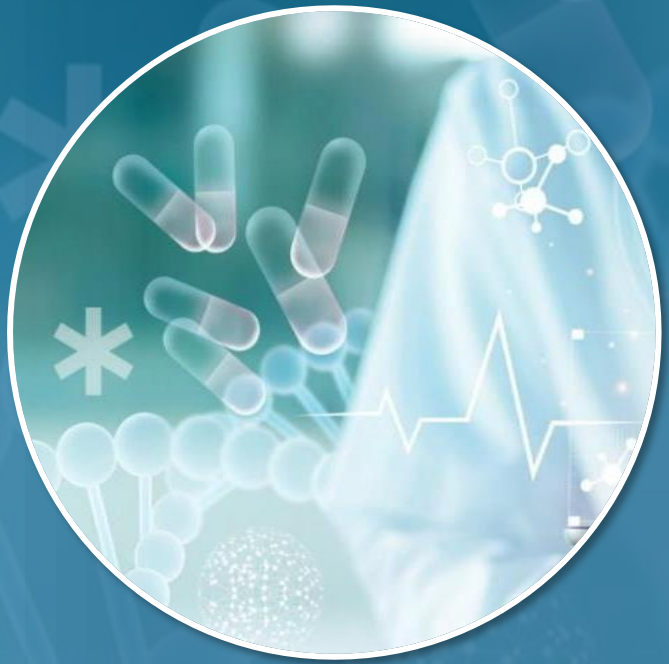


NAVIGATING FDA'S EXPECTATIONS FOR DRUG APPROVAL

Adaptive designs for dose-optimization and accelerated approval

- December 12th 2024
- Leandro Garcia-Barrado, Vaiva Deltuvaite-Thomas, Vincent Staggs & Elisabeth Coart

KEEPING UP WITH FDA REGULATIONS FOR DRUG DEVELOPMENT

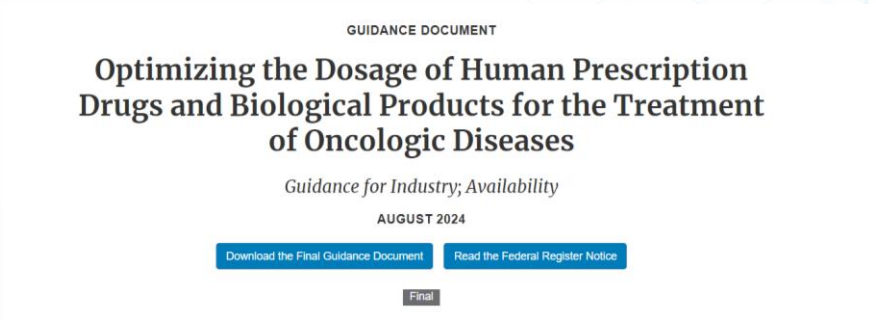
- Total of 43 newly added (draft/final) guidance documents[1] in 2024
- Total of 13 ongoing Center for Drug Evaluation and Research(CDER) initiatives[2]
- Pilot programs
- FDA designations for making drugs available as rapidly as possible: Fast track, breakthrough, priority review [3]
- Accelerated approval vs full approval pathway [3]
- FDA patient-focused drug development (PFDD) [4]
- …

[1] https://www.fda.gov/drugs/guidances-drugs/newly-added-guidance-documents
[2] https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/cder-initiatives
[3] https://www.fda.gov/patients/learn-about-drug-and-device-approvals/fast-track-breakthrough-therapy-accelerated-approval-priority-review
[4] https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical

NAVIGATING FDA'S EXPECTATIONS FOR DRUG APPROVAL

- From statistical perspective
- Through innovative trial design
- Focusing on
  - Project Optimus
  - Accelerated Approval pathway

PROJECT OPTIMUS
ONCOLOGY CENTER OF EXCELLENCE



https://www.fda.gov/about-fda/oncology-center-excellence/project-optimus
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/optimizing-dosage-human-prescription-drugs-and-biological-products-treatment-oncologic-diseases

CHALLENGES OF DOSE FINDING FOR TARGETED DRUGS

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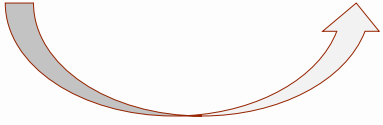
Cytotoxic chemotherapies	Targeted therapies
• Short treatment duration	• Continues until toxicity/PD
• Only most severe toxicities counted as DLT's	• Account for lower grade but chronic toxicities
• Serious toxicities occur early	• Serious toxicities may occur later
• Assume higher dosage means higher efficacy	• Higher dosage not necessarily means higher efficacy
• Goal: define MTD (Maximum Tolerated Dose)	• Goal: define OBD (Optimal Biological Dose)



Project Optimus

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Early clinical development - Dose-finding

1. Move away from Maximum Tolerated Dose (MTD)

2. Select Therapeutic Dose Range based on
   - Toxicity
   - Efficacy (signals)
   - PK/PD data
   - Long term tolerability

3. Integrate modeling and simulation with emerging clinical data

PROJECT OPTIMUS AND ITS IMPLICATIONS

What type of study designs should drug developers use for the dose-finding part?

- Clearly not “3+3”
- Modeling approach needed
  - Model-based designs
  - Model-assisted designs
  - Dose-escalation based on toxicity or several outcomes?
- How to select the therapeutic dose range for further evaluation?

Over to Vaiva...

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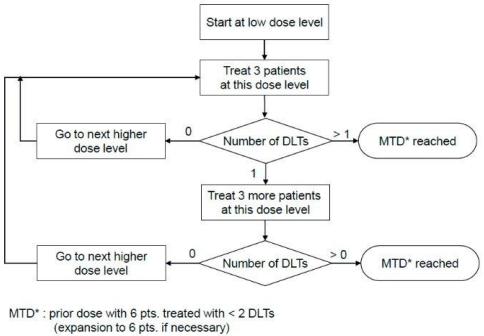
DOSE FINDING DESIGNS

3 + 3 DESIGN

- Advantages:
  - Simple and easy to implement
  - Does not require modelling
  - Offers conservative dose escalation for drugs with narrow therapeutic index
- Issues:
  - No formal statistical justification
  - Slow escalation with (too) many patients treated at subtherapeutic doses
  - Only information of the current dose-level used during dose-escalation
  - Imprecise estimates of MTD



MODEL-BASED DESIGNS

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Algorithm-based design

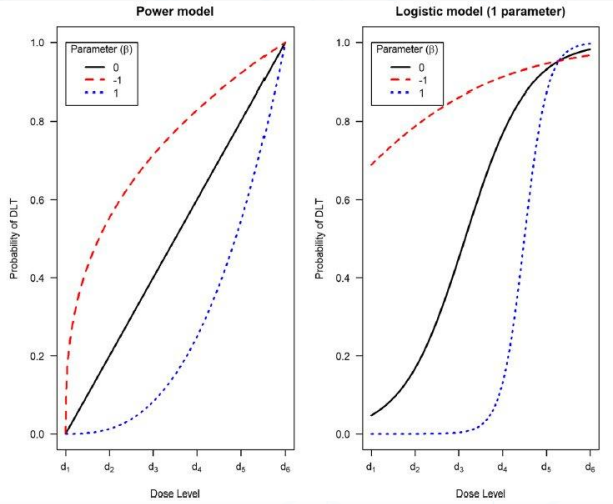
- Simple and easy to implement
- Imprecise estimates of MTD

Model-based design

- Superior performance
- Difficult implementation

CONTINUOUS REASSESSMENT METHOD (CRM)

- Advantages:
  - More precise MTD selection
  - More patients treated at optimal dose levels
  - Borrowing across dose levels
- Issues:
  - Difficult to understand
  - Difficult to implement
  - Needs frequent interaction between statisticians and clinicians



Wheeler et al., BMC Medical Research Methodology (2019)

MODEL-BASED DESIGNS

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Algorithm-based design

- Simple and easy to implement
- Imprecise estimates of MTD

Model-based design

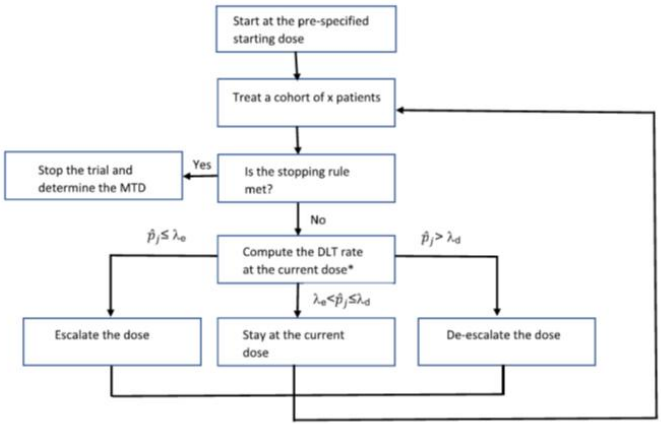
- Superior performance
- Difficult implementation

Model-assisted design

- Set of easy pre-tabulated rules after each patient cohort
- Based on sound statistical arguments

BAYESIAN OPTIMAL INTERVAL (BOIN) DESIGN

- Advantages:
  - More patients treated at therapeutic dose
  - More precise estimation of MTD
  - Accelerated titration possible
- Issues:
  - More involved to set-up
  - Simulations needed to investigate operating characteristics



Ananthakrishnan et al., Contemp Clin Trials Commun. 2022

CYTOTOXICS VS TARGETED AGENTS

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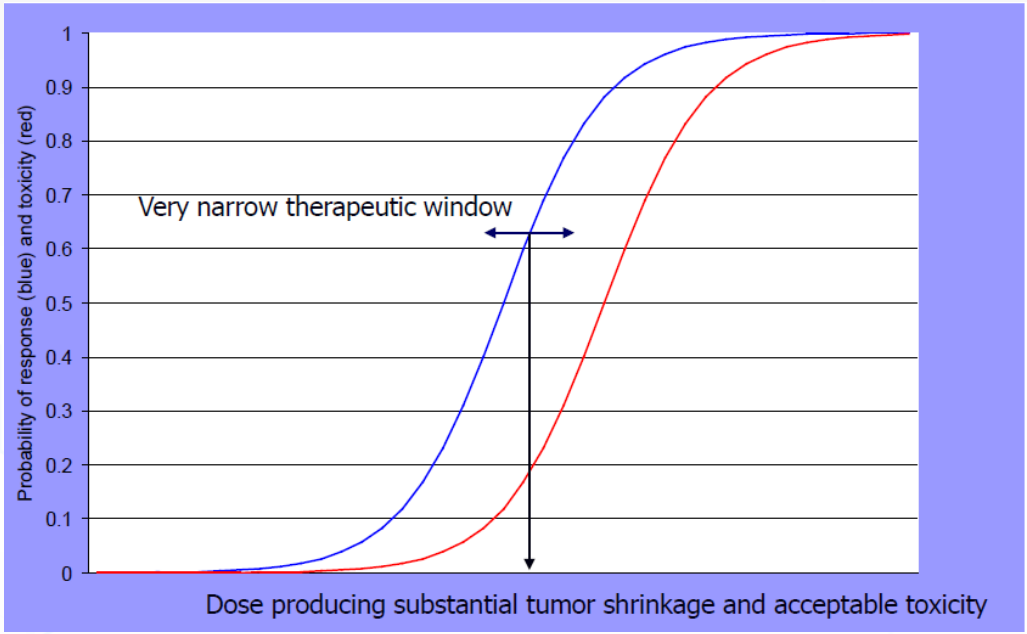
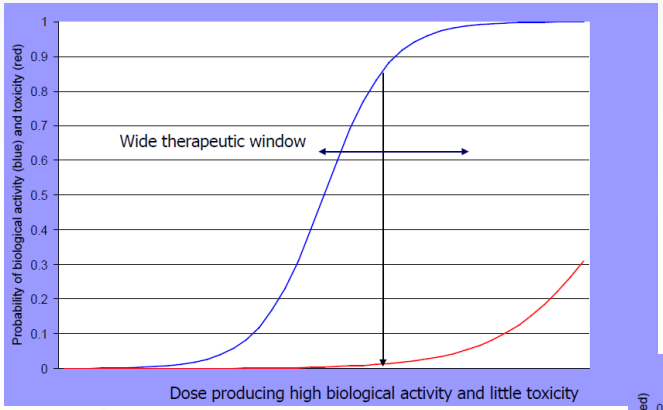
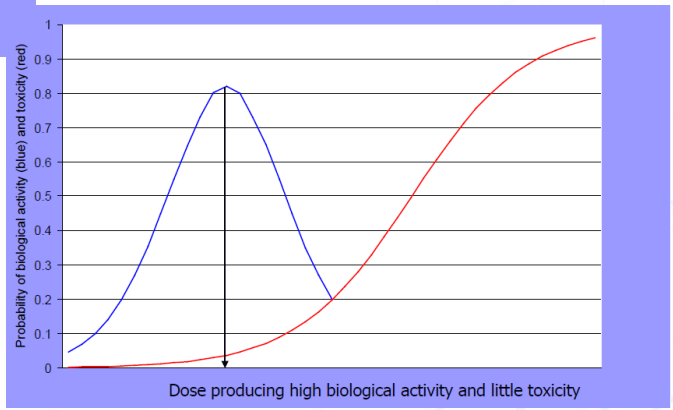
- Cytotoxics



CYTOTOXICS VS TARGETED AGENTS

- Targeted agents (biologics, therapeutic vaccines or immunotherapies, targeted therapies, small molecules, etc.)





TARGETED AGENTS

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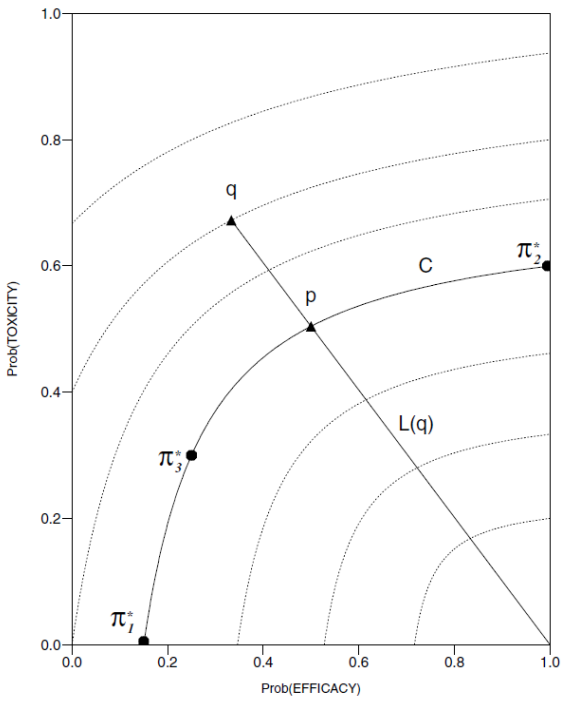
- Target dose: optimal biological dose (OBD)
- Need for efficacy-toxicity designs
  - Model-based: EffTox
  - Model-assisted: BOIN12, BOIN-ET, …

EFFICACY–TOXICITY TRADE-OFF (EFFTOX) DESIGN



Thall and Cook, Biometrics (2004)

- Assume some initial relationships for:
  - Dose-toxicity
  - Dose-efficacy
- Set utility contours
- After each cohort, update the dose-toxicity and dose-efficacy relationships and re-calculate utility scores for each dose
- Next cohort is assigned the dose with highest utility

BOIN12 DESIGN

- Assign utility weights based on clinicians' input
- After each cohort update desirability scores based on observed efficacy, toxicity and these weights
- Two-step decision process for dose escalation/de-escalation:
  - Check toxicity rate for safety
  - If the dose is deemed safe, next cohort is assigned the dose with highest utility

	Efficacy	
Toxicity	**Yes**	**No**
No	$u_1 = 100$	$u_2 = 40$
Yes	$u_3 = 60$	$u_4 = 0$

Lin et al., JCO Precis Oncol. 2020

BOIN-ET DESIGN

- As in BOIN12, the decisions are made based on the observed toxicity and efficacy rates at a current dose.
- However, the decisions are made based on the two dimensions simultaneously.

Dosing Decision Table for the BOIN-ET Design.

	$0 \leq \widehat{p}_j \leq \lambda_e$	$\lambda_e < \widehat{p}_j \leq \lambda_d$	$\lambda_d < \widehat{p}_j \leq 1$
$\eta_1 < \widehat{q}_j \leq 1$	Stay	Stay	De-escalate
$0 \leq \widehat{q}_j \leq \eta_1$	Escalate	Escalate/Stay/De-escalate	De-escalate

Ananthakrishnan et al., Contemp Clin Trials Commun. 2022

THE RECOMMENDED PHASE 2 DOSE

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- Optimal biological dose(s) (OBD)
- But also…
  - pharmacokinetics
  - pharmacodynamics
  - pharmacogenomics
  - long-term safety
  - etc…

SUMMARY

- Algorithm-based
  - Simple and easy to implement
  - Imprecise estimates of MTD
- Model-based
  - Superior performance
  - Difficult implementation
  - Extensions to include efficacy available
- Model-assisted
  - Set of easy pre-tabulated rules after each patient cohort
  - Based on sound statistical arguments
  - Extensions to include efficacy available

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Later clinical development – Dose-optimization

1. Pre-approval requirement
2. Randomization essentially mandatory to evaluate multiple dosages
3. Incorporate safety information beyond DLT's

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Randomization is crucial

- Potential of confounding in dose-selection trials
  - Differences in cohorts on different doses
- Will allow further unbiased characterizing of doses in terms of toxicity, efficacy, tolerability,…

PROJECT OPTIMUS AND ITS IMPLICATIONS

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- Will randomization increase cost and time for dose selection process?
  - It depends
    - Less (non-randomized) expansion cohorts
    - Randomized backfilling of doses?
    - No need to power dose-optimization trial for dose comparison
    - Use innovative trial designs!

PROJECT OPTIMUS AND ITS IMPLICATIONS

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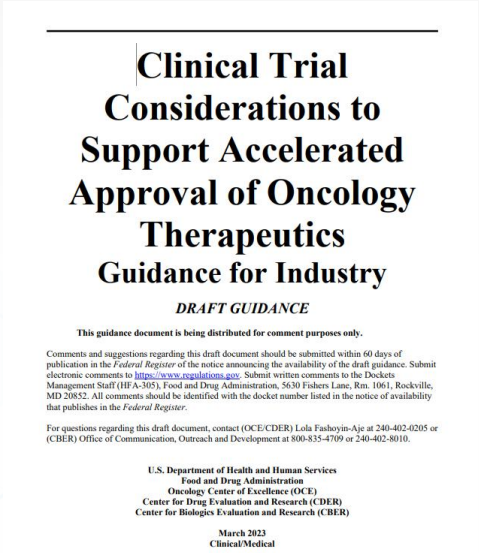
- Use innovative trial designs!
  - Can randomized dose-optimization be included in seamless phase 2/3 trial?
    - How to size the dose-optimization phase?
    - Decision framework for dose selection?
    - Efficacy endpoint for dose selection?
  - Can this trial combine objectives of dose-optimization and approval?
    - Early efficacy endpoint used for dose-selection appropriate for accelerated approval?

ACCELERATED APPROVAL PATHWAY



Clinical Trial Considerations to Support Accelerated Approval of Oncology Therapeutics

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (OCE/CDER) Lola Fashoyin-Aje at 240-402-0205 or (CBER) Office of Communication, Outreach and Development at 800-835-4709 or 240-402-8010.

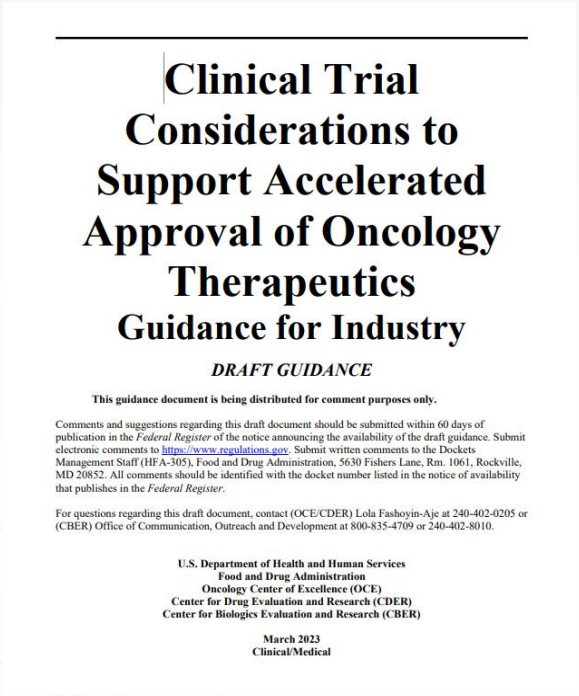
U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

March 2023
Clinical/Medical

- Allows drugs for serious conditions filling an unmet medical need to be approved based on a surrogate endpoint/intermediate clinical endpoint

- Draft guidance 2023
  - Confirmatory trial expected to be (close to) fully enrolled
  - Two strategies for confirmatory trial to establish clinical benefit
    - Phase 2 trial for accelerated approval followed by confirmatory phase 3 trial
    - “One trial” approach: Seamless phase II/III trial

ACCELERATED APPROVAL PATHWAY



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March 2023
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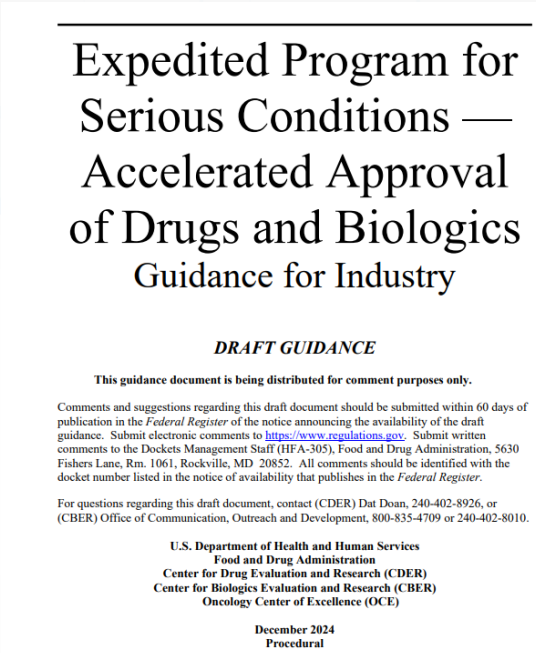

Expedited Program for Serious Conditions — Accelerated Approval of Drugs and Biologics

Guidance for Industry

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

December 2024
Procedural

Over to Leandro...

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ONE TRIAL TO RULE THEM ALL

FANTASY OR REALITY?

OVERVIEW

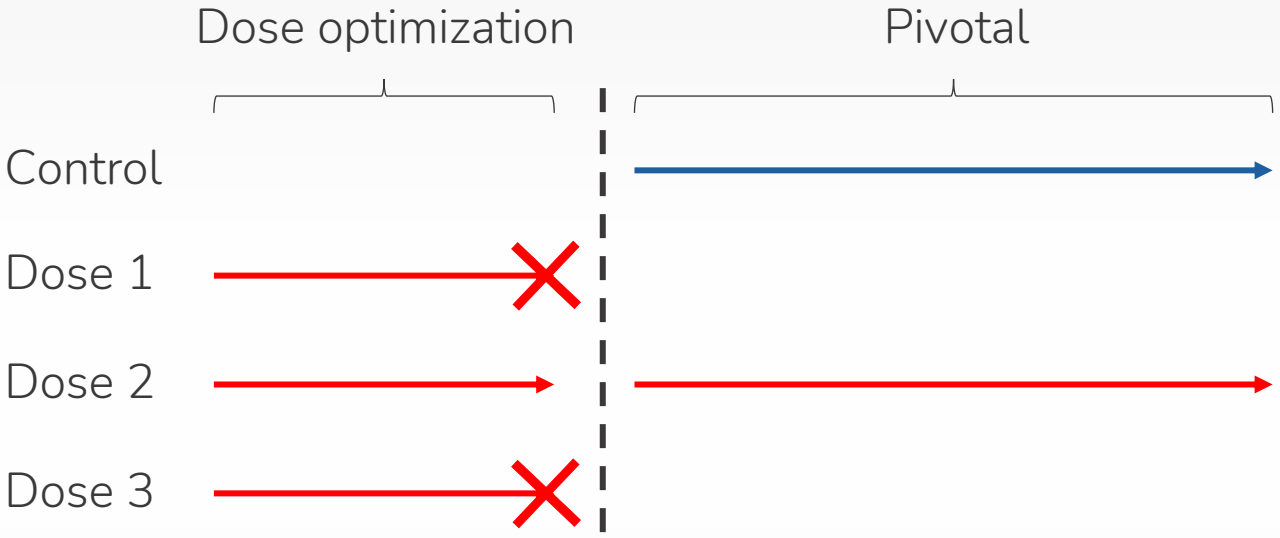
- Seamless dose optimization pivotal trial
- Decision options?
  - Formal test (alpha splitting)
  - Group Sequential Design
  - General adaptive design
- Early endpoint-based decisions
- Accelerated Approval
- X-course dinner or all-you-can-eat buffet?

SEAMLESS DOSE OPTIMIZATION PIVOTAL TRIAL

- Starting point
  - Successfully performed a dose finding trial
  - Incorporated all available information
  - Selected a set of doses to consider in a dose optimization trial
- Question: What to do next?
  - Select the optimal dose?
  - Pivotal trial?
  - Shortcuts?

SEAMLESS DOSE OPTIMIZATION PIVOTAL TRIAL

- Operationally seamless

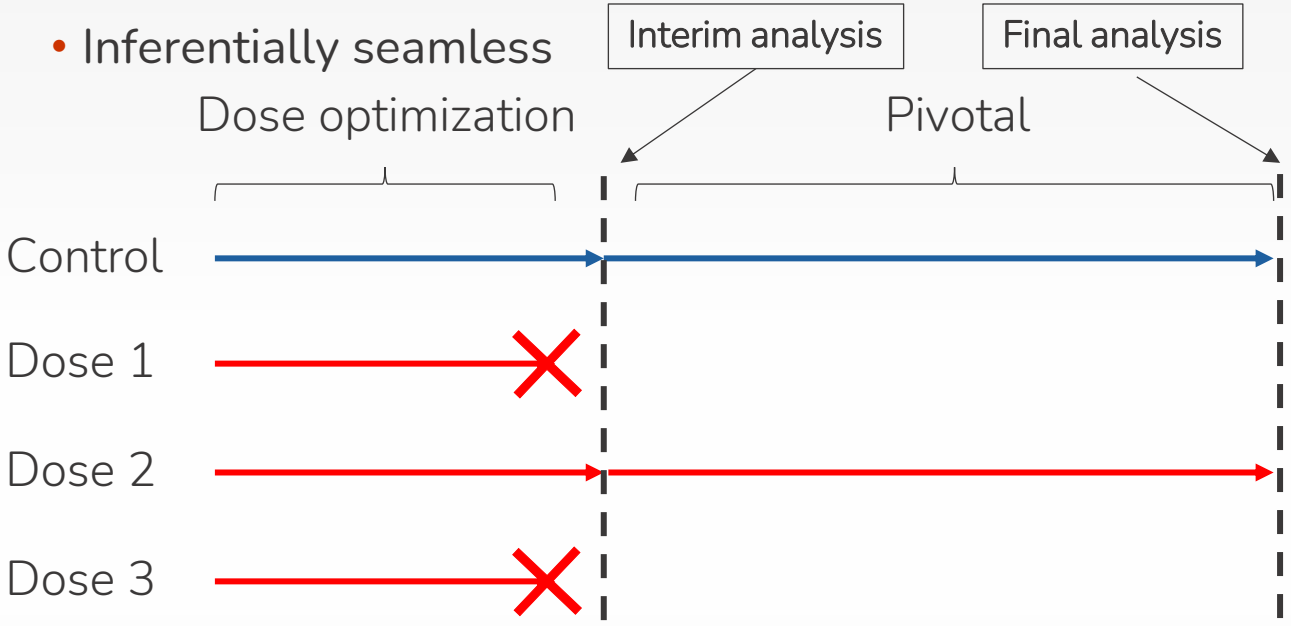


- Straightforward type-I error control
- No 'need' for control group in optimization
- Allow time between trials (longer term toxicities/tolerability)

- No way to include dose 2 information from optimization trial
- No 'calibration' information
- Need some time between trials

SEAMLESS DOSE OPTIMIZATION PIVOTAL TRIAL

- Inferentially seamless



- Available calibration information
- Include Dose 2 patients in Pivotal trial
- Shorter combined trial duration

- Type-I error control needed
- Control group required in optimization
- Reduced time between 'trials'
  (longer term toxicities/tolerability)

OVERVIEW

- Seamless dose optimization pivotal trial
- Decision options?
  - Formal test (alpha splitting)
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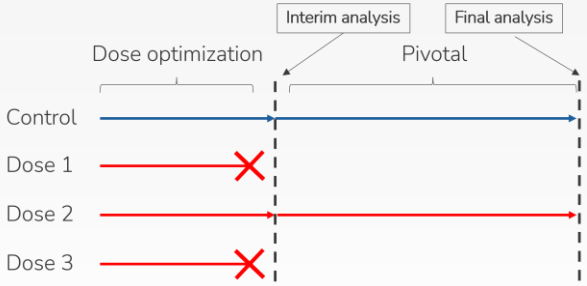
FORMAL TEST (ALPHA SPLITTING)

- Multiple comparisons
  - Each dose vs control
- Choose the correction of your choice
  - I.e. ≈splitting α over dose comparisons



- Multiple testing within the selected dose arm
  - Hierarchical testing: within dose arm carry over considered α-level
- In Pivotal trial use allocated α to your liking
  - Fixed sample size
  - Group-sequential
  - Adaptive

OVERVIEW

- Seamless dose optimization pivotal trial
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  - Group Sequential Design
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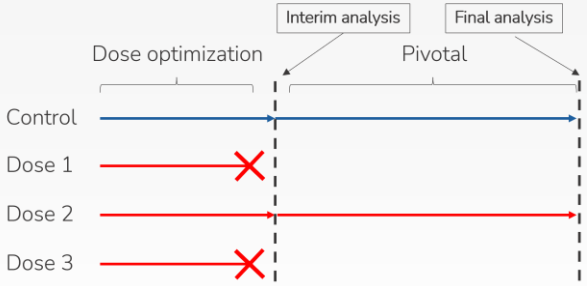
GROUP SEQUENTIAL DESIGN

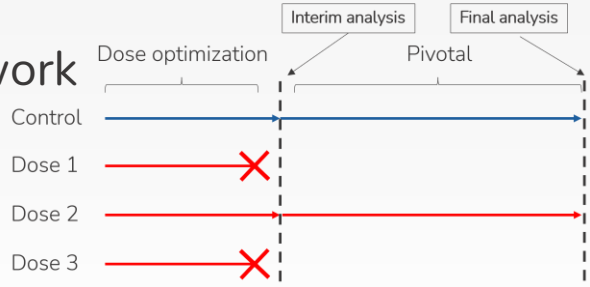
- Stallard, N., and Todd, S. 2003
- Calculate score statistics at dose optimization interim



- Pick the dose with the maximum value to 'graduate' to pivotal trial
  - Allows for early stopping
  - Choosing other dose will decrease power
- Type-I error control
  - Calculating critical values for subsequent decisions based on theoretical joint-distribution of test-statistics

GROUP SEQUENTIAL DESIGN

- Embedded in theoretical framework
  - Efficient under normality assumption
- Allows additional interim analyses after dose selection
- Good in selecting ‘one of the best’
- All interim analyses need to be pre-specified



OVERVIEW

- Seamless dose optimization pivotal trial
- Decision options?
  - Formal test (alpha splitting)
  - Group Sequential Design
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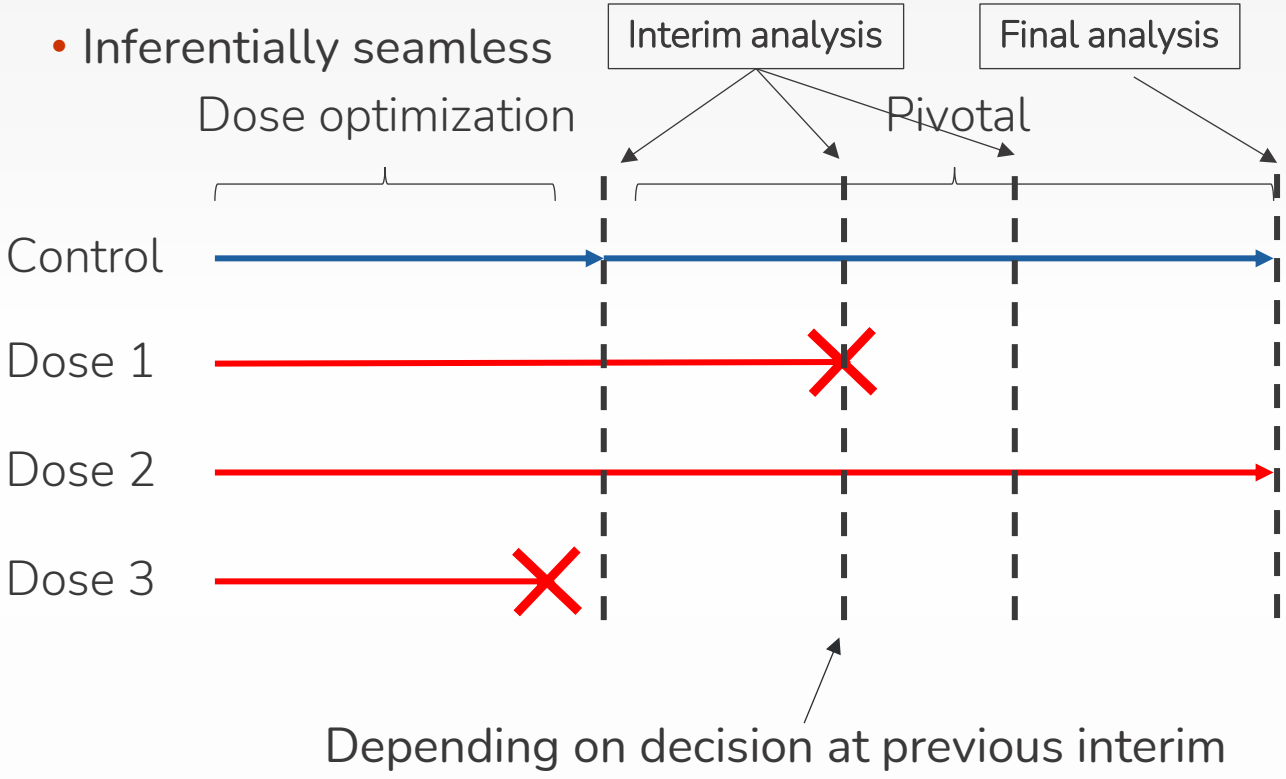
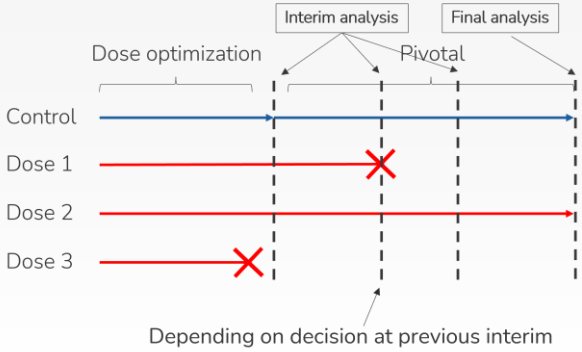
- X-course dinner or all-you-can-eat buffet?

- Inferentially seamless



GENERAL ADAPTIVE DESIGNS

- Unplanned adaptations can be incorporated



- Invokes the closed testing principle
  - Account for multiple comparisons by adjusted stage-wise p-values

- P-value combination tests
  - Decisions at multiple stages

OVERVIEW

- Seamless dose optimization pivotal trial
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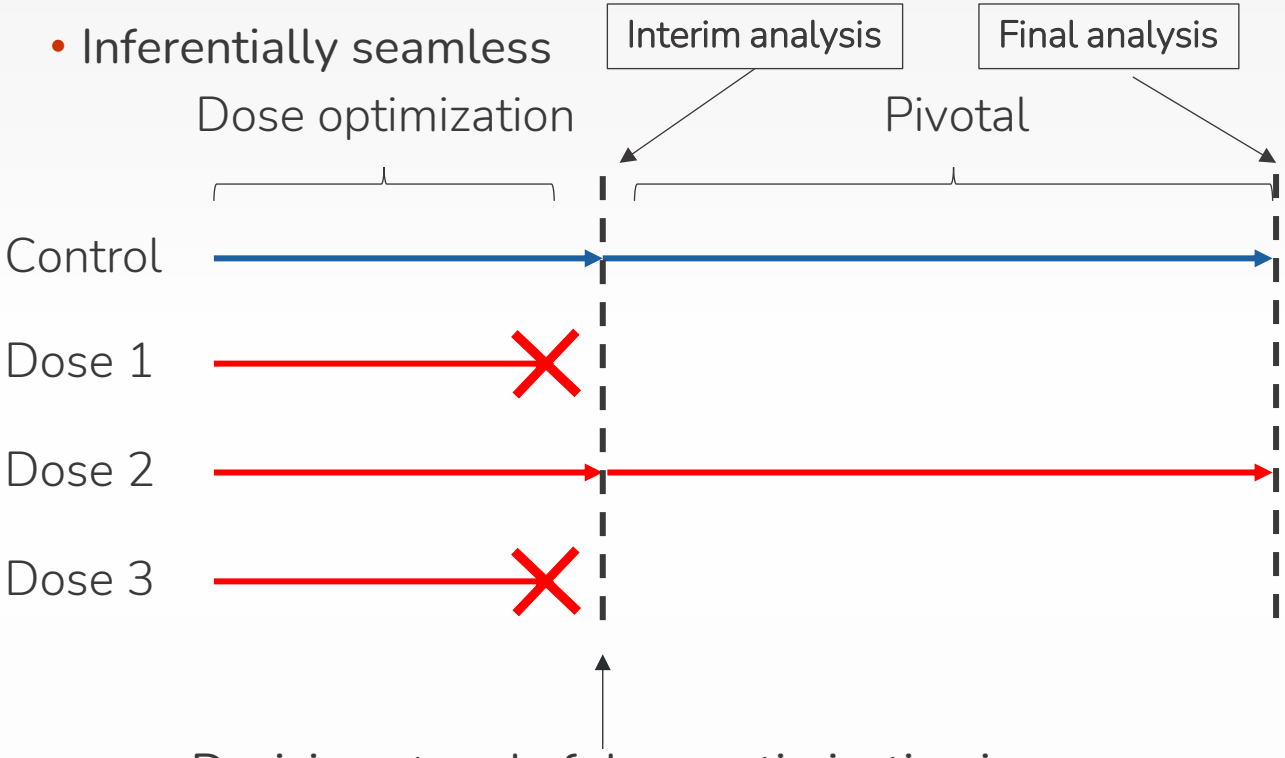
EARLY ENDPOINT-BASED DECISIONS

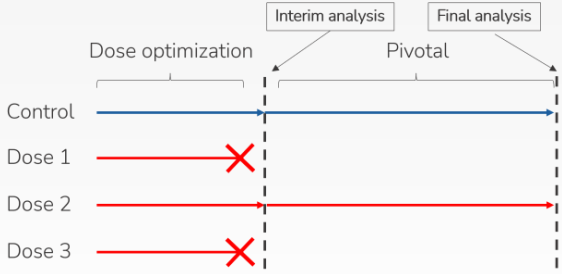
- Inferentially seamless



EARLY ENDPOINT-BASED DECISIONS

- Todd, S., and Stallard, N. 2005

- Calculate score statistics at dose optimization interim



- Pick the dose with the maximum value to 'graduate' to pivotal trial
  - Allows for early stopping
  - Choosing other dose will decrease power

- Type-I error control
  - Calculating critical values for subsequent decisions based on theoretical joint-distribution of test-statistics
  - **Correlation between the test statistics based on the early and final endpoint!**

OVERVIEW

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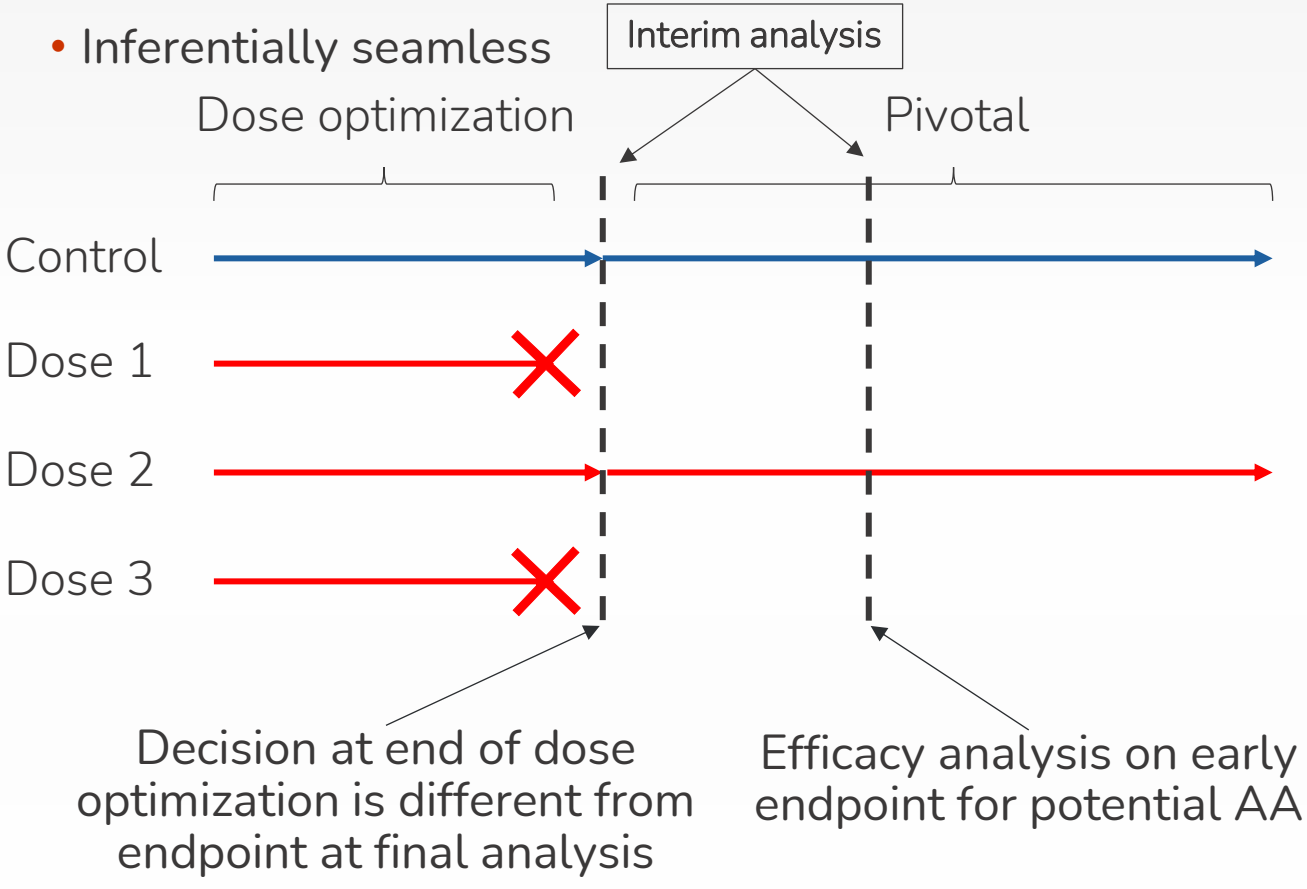
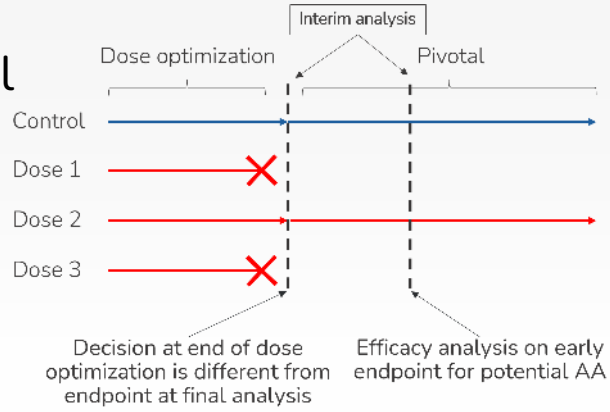
ACCELERATED APPROVAL

- Inferentially seamless



ACCELERATED APPROVAL

- Single-trial accelerated approval
- Account for multiple testing
  - AA interim analysis
  - Final analysis
- Hierarchical testing (all-in)
  - Only proceed when significant interim
- Fallback procedure
  - ‘Reserve’ some type-I error probability to spent at final
  - Trial may continue even when no significant interim



OVERVIEW

- Seamless dose optimization pivotal trial
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  - Group Sequential Design
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- Early endpoint-based decisions
- Accelerated Approval
- X-course dinner or all-you-can-eat buffet?

X-COURSE DINNER OR ALL-YOU-CAN-EAT BUFFET

- No need to re-invent the wheel
  - Already many options in terms of methodology
  - Exciting times for methodologists
- Seamless optimization – pivotal trial
  - Trade-off in efficiency (sample size)
    - Correction in dependence test-statistics
    - Being able to incorporate dose optimization information
    - Gets worse when considering 'early-endpoint'

X-COURSE DINNER OR ALL-YOU-CAN-EAT BUFFET

- Accelerated approval
  - Operationally sensible
    - Enough information at optimal dose selection?
    - Regulatory requirements (almost finalized accrual)
- Seamless all the way
  - Integration of 'all' information may not be straightforward
- No one-size fits all solution
  - Most efficient/optimal design is defined on a case-by-case basis
- Don't make things more complex than needed

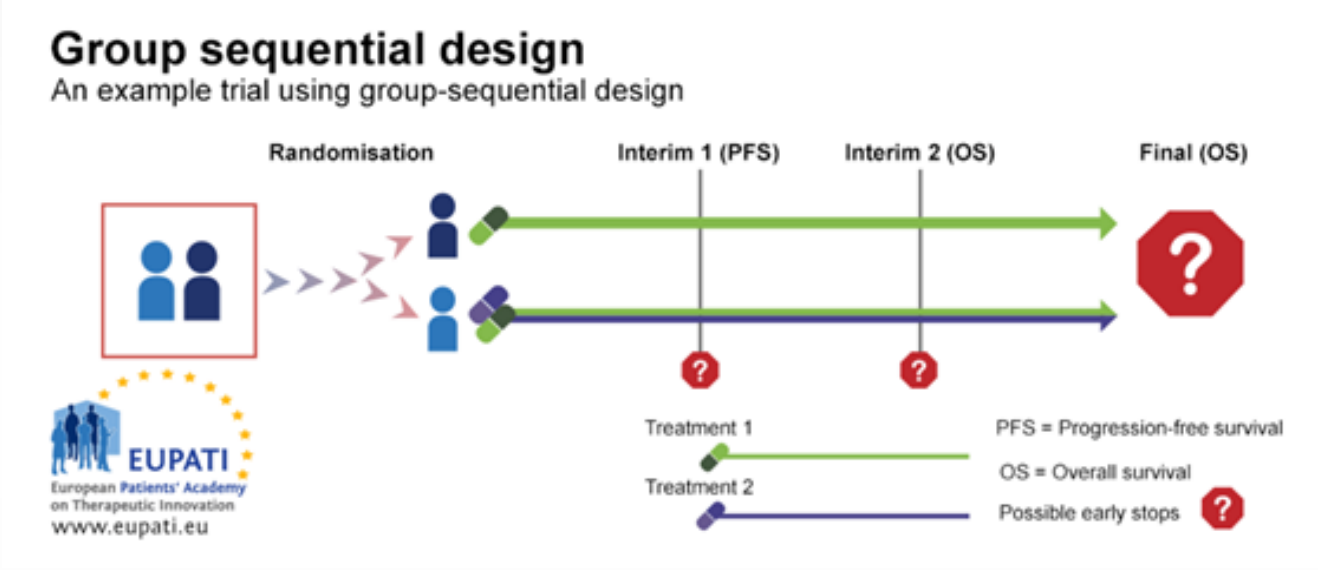
GROUP SEQENTIAL DESIGNS (GSD) AND SAMPLE SIZE RE-ESTIMATION

- GSD: Introduce interim analyses for flexibility
  - Early stopping for efficacy
  - Early stopping for futility
  - Reduces the expected sample size of the trial

  - Especially of interest when a large trial is designed with limited prior information
    - Early stop if treatment effect is larger than anticipated
    - Continue until end if needed
    - Eg: Seamless phase II/III trial

GROUP SEQENTIAL DESIGNS (GSD) AND SAMPLE SIZE RE-ESTIMATION

- GSD: Introduce interim analyses for flexibility



GROUP SEQENTIAL DESIGNS (GSD) AND SAMPLE SIZE RE-ESTIMATION

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- GSD: Efficient designs
  - Powered for conservative treatment effect
  - Total (maximum) sample size is large
  - Expected sample size is smaller

- Sample size re-estimation
  - Powered for an optimistic treatment effect
  - Smaller initial sample size
  - Sample size increased if needed, based on interim treatment effect

GROUP SEQENTIAL DESIGNS (GSD) AND SAMPLE SIZE RE-ESTIMATION

- Is sample size re-estimation as efficient as GSD?
- When is sample size re-estimation the better design?
- Methodology??

- Over to Vince…

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ADAPTIVE DESIGNS: SAMPLE SIZE REASSESSMENT

SAMPLE SIZE REASSESSMENT

- Adaptive design: final sample size not pre-determined
- Sample size reassessment (SSR)
  - Choose final sample size based on interim analysis
  - Types
    - Blinded—e.g., estimate nuisance parameter(s)
    - Unblinded—e.g., estimate treatment effect

SAMPLE SIZE REASSESSMENT

- Unblinded SSR for treatment effect
- Type I error rate inflation?
  - Depends on conditional power at interim
  - Conditional power >50%: no adjustment required
  - Various adjustments available

PROMISING ZONE DESIGNS

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Increase final sample size *if and only if* interim statistic falls in a prespecified “promising” range

CONSTRAINED PROMISING ZONE DESIGN

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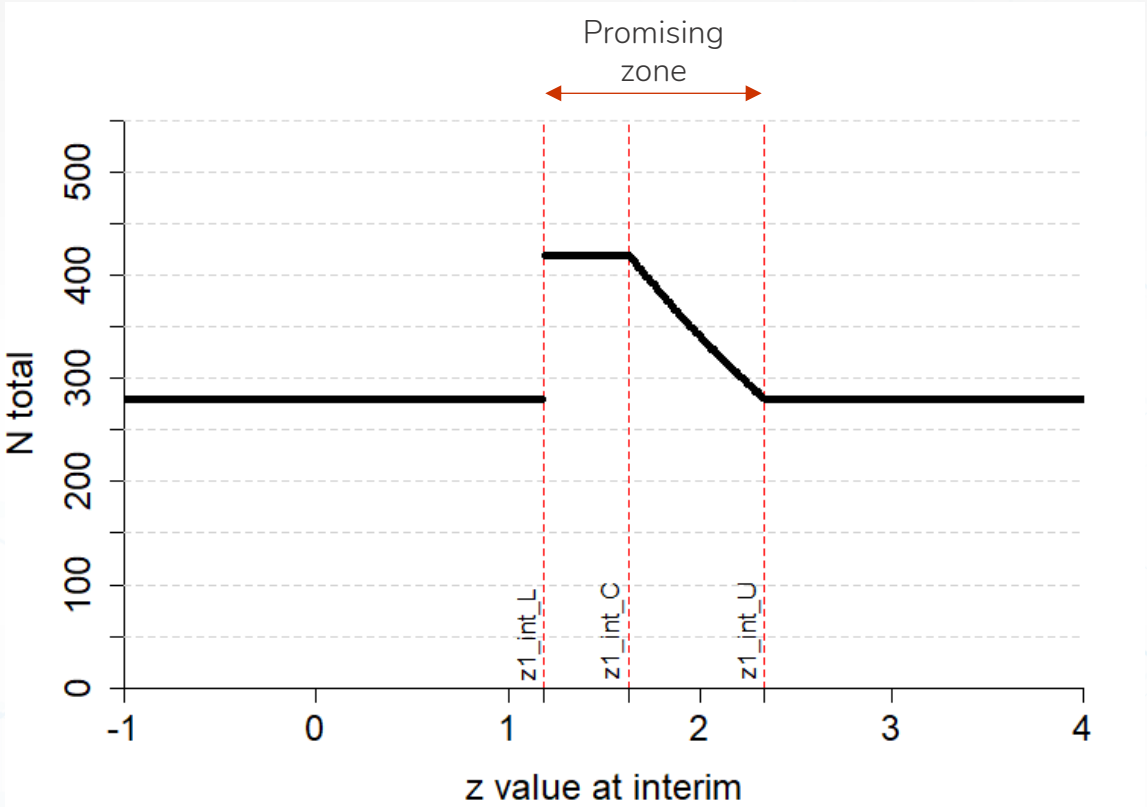
Three possibilities at interim

- Unfavorable/disappointing: effect too weak to merit sample size increase
- Favorable: strong effect; sample size increase unnecessary
- Promising: effect somewhere between unfavorable and favorable

SEE HSIAO ET AL. FIGURE 1



CONSTRAINED PROMISING ZONE DESIGN

- On test statistic scale, promising zone may be rather narrow
- Prob(sample size increase) may be 25-50%
- No increase for unpromising interim results, but less power for such results means lower power overall

NAVIGATING FDA'S EXPECTATIONS FOR DRUG APPROVAL

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- Project Optimus : Many implications for dose selection
  - Maximum Tolerated Dose ⇨ Optimal Biological Dose
  - Therapeutic range: randomized comparison required for >1 dose
  - Dose selection based on toxicity, PK, PD, efficacy, tolerability
  - Pre-approval

- Project Optimus: Many opportunities for dose selection
  - Modeling of available clinical data
  - No one-size fits all approach
  - Include in 'One-trial' approach accelerated approval?
  - Trial design is key!!

NAVIGATING FDA'S EXPECTATIONS FOR DRUG APPROVAL

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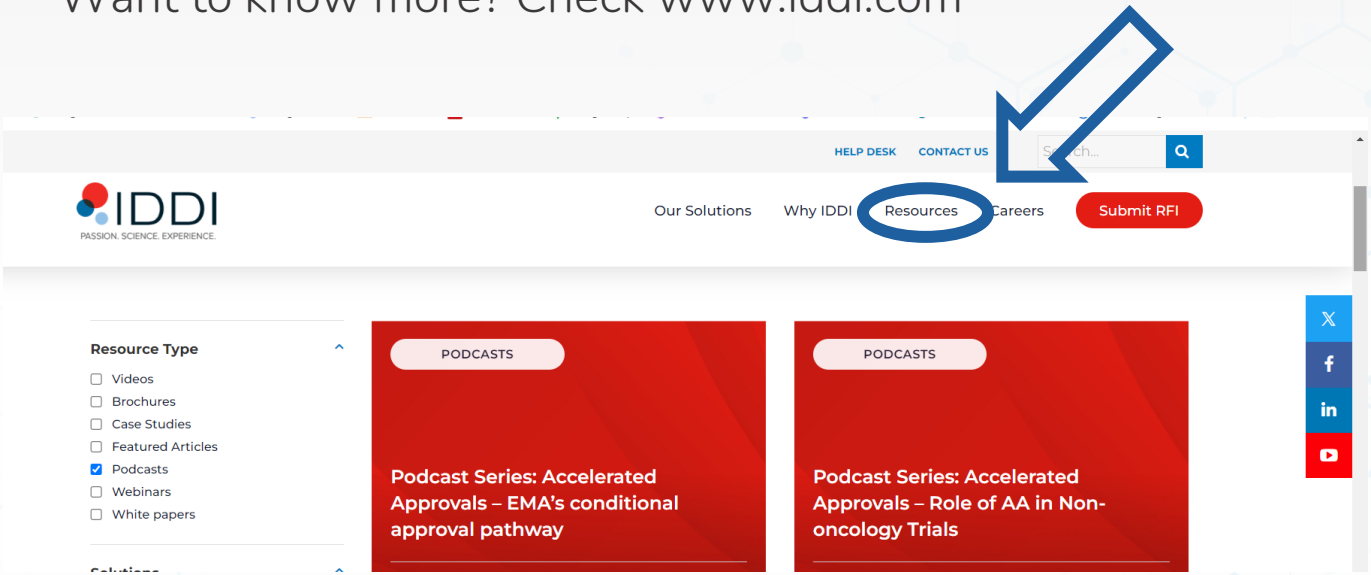

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THANK YOU!

Questions ?