Interim Analysis and Adaptive Design

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Clinical Trial

- A prospectively planned experiment for the purpose of evaluating a potentially beneficial therapy or treatment
- Conducted under as many controlled conditions as possible so that they provide definitive answers to pre-determined, well-defined questions
- Classic design requires such parameters to be pre-specified and fixed throughout a clinical trial
  - Sample size
  - Randomization ratio
  - Number of study arms
  - ... ...

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Adaptations in Clinical Trial

Sometimes are necessary to

- reflect real medical practice on the actual patient population with the disease under study
- increase the probability of success for identifying clinical benefit of treatment

Include but not limited to

- Modifications of inclusion/exclusion criteria
- Adjustment of study dose or treatment
- Extension of study duration
- Changes in study endpoints
- Modifications in study design based on interim analysis

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Interim Analysis (IA)

- *"Any examination of data obtained in a study while that study is still ongoing, and is not restricted to cases in which there are formal between-group comparisons"* – FDA Guidance on Adaptive Design (2010)
- Reasons for interim analysis
  - Ethical
  - Administrative
  - Economic
- Types of interim analysis
  - Efficacy vs. Safety vs. Other
  - Blinded vs. Unblinded
- Multiple stages are formed with interim analysis

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Adaptive Design

- *"A study design that includes a prospectively planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data"* – FDA Guidance on Adaptive Design (2010)
- Adaptations based on interim analysis
  - Dose escalation/de-escalation
  - Early stopping for superiority or futility
  - Sample size re-estimation
  - Outcome-adaptive randomization
  - Study population enrichment
  - Drop or add study arms
  - ... ...

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Types of Adaptive Designs

- Adaptive Dose-Finding Design
- Group Sequential Design
- Sample Size Re-estimation
- Adaptive Randomization Design
- Drop-Loser and/or Add-Arm Design
- Biomarker-Adaptive Design
- . . . . . .
- Bayesian Design

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Statistical Aspects

- Type I error – α control and determination of stopping boundaries
- Type II error – β control and calculation of power or sample size
- Trial monitoring – make decisions based on conditional power (or futility index)
- Analysis after completion of study – calculation of adjusted p-values, unbiased point estimates and confidence intervals

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Pro's and Con's

adaptive-pros-and-cons-2.jpg

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Group Sequential Design (GSD)

group-sequential-design-v11_EN.png

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A Phase III NSCLC Trial

Consider to design a phase III clinical trial for an experimental therapy vs. standard chemotherapy (control) in non-small cell lung cancer (NSCLC) patients, the primary endpoint is overall survival (OS)

- $OS_{ctrl} = 12$ *months*
- The clinically meaningful effect size $HR = 0.75$, (i.e. $OS_{trt} = 16$ *months*)
- Type I error $\alpha = 2.5\%$ (one-sided)
- Power $1 - \beta = 90\%$
- Accrual period of 48 months
- Minimum follow-up period of 12 months

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Classic Design with Fixed Sample Size

- Pre-specify accrual and drop out rates
- Total study duration is at least 60 months!
- Sample size
  - Required number of events is 507
  - Required number of patients is 718
- No (formal) interim analysis
- Must wait till the study end to analyze data and make decisions

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GSD with Interim Analysis

Can we evaluate efficacy results earlier to make decisions?

- If the experimental therapy truly works, can we complete study early to claim efficacy? – Superiority
- If the experimental therapy does not work, can we terminate study early to avoid harmful patient exposure? – Futility

Solution: Group sequential design with interim analysis

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GSD with Interim Analysis

- How many interim analysis?
  - Not too many as interim analysis takes time and efforts
- When to conduct interim analysis?
  - Not too early as information may be too limited for making decisions, at least 25%–35%
  - Not too late (relative to study duration) as benefit of interim analysis diminishes
- Types of interim analysis?
  - Superiority only
  - Futility only
  - Both superiority and futility (binding vs. non-binding)

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Statistical Issues

- Repeated significance testing with interim analysis
  - Claim efficacy after 1st interim analysis
  - Claim efficacy after 2nd interim analysis if study continues after 1st interim analysis
  - .....
  - Claim efficacy after final analysis if study continues after all interim analysis
- Multiple looks of superiority inflate family-wise error rate (FWER) of type I error (introduce bias)
- Multiple looks of futility inflate FWER of type II error (decrease power)
- Implementation of interim analysis for confirmatory trials must be done by an independent data monitoring committee (IMDC)

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GSD for NSCLC Trial

Consider to modify the classic design for NSCLC trial to a group sequential design with

- One interim analysis at 50% information (i.e. number of events)
- Both superiority and futility at interim analysis
- FWER control methods
  - Pocock bounds
  - O'Brien-Fleming bounds
  - Spending function approach (Hwang-Shih-DeCani family)

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GSD with Pocock Bounds

- Terminate study for superiority if $HR \leq 0.79$ at interim analysis
- Terminate study for futility if $HR \geq 0.89$ at interim analysis
- Continue study if $0.79 < HR < 0.89$ at interim analysis
- Claim efficacy if $HR \leq 0.84$ after final analysis
- Required number of events increases (from 507) to 637

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GSD with Pocock Bounds

Analysis	Value	Efficacy	Futility
IA 1: 50%	Z	2.1570	1.0313
N: 768	p (1-sided)	0.0155	0.1512
Events: 319	HR at bound	0.7852	0.8908
Month: 36	P(Cross) if H_0 true (HR=1)	0.0155	0.8488
	P(Cross) if H_1 true (HR=0.75)	0.6600	0.0620
Final	Z	2.2010	2.2010
N: 902	p (1-sided)	0.0139	0.0139
Events: 637	HR at bound	0.8399	0.8399
Month: 60	P(Cross) if H_0 true (HR=1)	0.0229	0.9771
	P(Cross) if H_1 true (HR=0.75)	0.9000	0.1000

- Approx. 66% chance to claim superiority at IA if therapy is efficacious
- Approx. 85% chance to claim futility at IA if therapy is not efficacious
- Duration of study reduced to 36 months if either superiority or futility is claimed at IA

GSD with O'Brien-Fleming Bounds

- Terminate study for superiority if $HR \leq 0.69$ at interim analysis
- Terminate study for futility if $HR \geq 0.97$ at interim analysis
- Continue study if $0.69 < HR < 0.97$ at interim analysis
- Claim efficacy if $HR \leq 0.84$ after final analysis
- Required number of events increases (from 507) to 520

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GSD with O'Brien-Fleming Bounds

Analysis	Value	Efficacy	Futility
IA 1: 50%	Z	2.9626	0.2670
N: 626	p (1-sided)	0.0015	0.3947
Events: 260	HR at bound	0.6923	0.9674
Month: 36	P(Cross) if H_0 true (HR=1)	0.0015	0.6053
	P(Cross) if H_1 true (HR=0.75)	0.2604	0.0200
Final	Z	1.9686	1.9686
N: 736	p (1-sided)	0.0245	0.0245
Events: 520	HR at bound	0.8413	0.8413
Month: 60	P(Cross) if H_0 true (HR=1)	0.0243	0.9757
	P(Cross) if H_1 true (HR=0.75)	0.9000	0.1000

- Approx. 26% chance to claim superiority at IA if therapy is efficacious
- Approx. 61% chance to claim futility at IA if therapy is not efficacious
- Duration of study reduced to 36 months if either superiority or futility is claimed at IA

Pocock vs O'Brien-Fleming Bounds

Design Parameters	Pocock	O'Brien-Fleming
HR bounds at IA	(0.79, 0.89)	(0.69, 0.97)
α spending at IA	0.0155	0.0015
Pr(stop for superiority) at IA	66%	26%
Pr(stop for futility) at IA	85%	61%
Events/Sample Size	637 / 902	520 / 736

- Pocock bounds spends more α at IA , thus more aggressive to claim superiority/futility
- O'Brien-Fleming bounds is more conservative in claiming efficacy/futility at IA, reserving more α for final analysis
- O'Brien-Fleming bounds requires fewer event/sample size than that of Pocock bounds

Flexible GSD with Spending Function

- Balance of aggressive/conservative IA
- Spending α as a function of the observed information levels
- Interim analysis may occur at any times with spending function
- Number of interim analyses may change
- Operational and logistical restrictions

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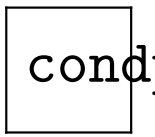
Conditional Power

Given a normal test statistic from IA, the conditional power curves under observed effect size (ES), H_0 and H_1



- Probability of rejecting H_0 (claim efficacy) during the rest of the trial based on accumulated data at IA
- Commonly used for monitoring an ongoing trial
- Maybe utilized for sample size re-estimation

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Sample Size Re-estimation

promising.jpg

[3]

[3] Cytel Presentation (2012)

Sample Size Calculation

- Sample size calculation based on early phase trial results or historical data at the design stage
  - A clinically meaningful effect size
  - Variability associated with the effect size (and other nuisance parameters)
- What if the effect size and/or the associated variability were incorrectly specified in the NSCLC trial?
  - If $OS_{ctrl} = 15$ months and $OS_{trt} = 20$ months (still HR=0.75)
  - number of event 507, sample size 795 to achieve 90% power
  - If $OS_{ctrl} = 12$ months and $OS_{trt} = 15$ months (HR=0.80)
  - number o event 844, sample size 1300 to achieve 90% power

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Sample Size Re-estimation

Can we plan a sample size re-estimation after interim analysis to overcome under-power or over-power in initial design of the NSCLC trial?

- If the study is under-powered based on interim analysis, increase sample size
- If the study is over-powered based on interim analysis, reduce sample size (though rarely done)

Solution: Sample size re-estimation after interim analysis

- N-adjusted clinical trial design (straightforward)
- Integrated with group sequential design (complex)
- Types of sample size re-estimation based on interim analysis
  - Blinded
  - Unblinded

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Blinded SSR for NSCLC Trial

Consider to modify the classic design for NSCLC trial to a sample size re-estimation design with

- Sample size re-estimation after an interim analysis at 50% information (i.e. number of events)
- Interim analysis is blinded without any knowledge of treatment assignment
- Interim analysis is not intended for superiority or futility
- Significance level does not need to be adjusted for blinded interim analysis

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Blinded SSR for NSCLC Trial

- Specified maximum sample size inflation was 100%
- Assumed enrollment overrun at interim analysis was 25 patients
- Observed unblinded median $OS = 17.5$ months at the interim analysis
- A heuristic calculation

Stage	IA	FA	SSR
No. of Events	254	507	507
Sample Size	359	718	794
Overrun	25	0	0

- Hence, blinded SSR suggest to increase sample size (initial design) by $794 - 718 = 76$ patients for final analysis (FA)

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Unblinded SSR for NSCLC Trial

- May provide more accurate sample-size estimation based on the estimated effect size at interim analysis
- Bias results from knowledge of observed effect size at interim analysis
- Statistical approaches to control FWER
  - Combination test
  - Conditional error function
  - Conditional power (CP)

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GSD with Unblinded SSR

Table: Asymmetric two-sided group sequential design with non-binding futility bound, sample size 833. Efficacy bounds derived using a HSD spending function with gamma = -4. Futility bounds derived using a HSD spending function with gamma = 1.

Analysis	Value	Efficacy	Futility
IA 1: 50%	Z	2.7500	0.9316
N: 417	p (1-sided)	0.0030	0.1758
	HR at bound	0.7257	0.8971
	P(Cross) if HR=1	0.0030	0.8242
	P(Cross) if HR=0.75	0.3889	0.0622
Final	Z	1.9811	1.9811
N: 833	p (1-sided)	0.0238	0.0238
	HR at bound	0.8493	0.8493
	P(Cross) if HR=1	0.0211	0.9789
	P(Cross) if HR=0.75	0.9000	0.1000

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GSD with Unblinded SSR

- Maximum sample size inflation is specified as 100%
- Assumed enrollment overrrun at IA is 25 patients
- Promising zone in CP interval $(0.36, 0.9)$ where SSR to be conducted

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GSD with Unblinded SSR

ssr.pdf

GSD with Unblinded SSR

Based on the GSD with interim analysis for superiority and futility

- Futility – Stop after interim analysis with actual sample size of 417
- Superiority – Stop after interim analysis with actual sample size of 417

Otherwise, based on the conditional power at the interim analysis,

- CP < 0.36 unfavorable – Continue the study after interim analysis without SSR, sample size is still 833
- CP $\in [0.36, 0.9]$ promising zone – Increase sample size $833 < N^* \leq 833 \times 2 = 1666$
- CP > 0.9 favorable – Continue the study after interim analysis without SSR, sample size is still 833

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Blinded vs. Unblinded SSR

Design Parameters	Blinded	Unblinded
FWER Control	No adjustment	Adjustment
Stat Methods	Straightforward	Complex
Implementation	In-house	External
FDA guidance	Well-understood	Less well-understood

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Regulatory Guidelines

- PhRMA (2006) – Adaptive designs in clinical drug development - an executive summary of the PhRMA working group
- EMA (2007) – Reflection paper on methodological issues in confirmatory clinical trials planned with an adaptive design
- FDA (2010) – Guidance for the use of Bayesian statistics in medical device clinical trials
- FDA (2010) – Adaptive design clinical trials for drugs and biologics
- FDA (2015) – Adaptive designs for medical device clinical studies

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FDA Draft Guideline 2010

- Distributed in February, 2010, expect to publish final document in 2017
- Endorsed by both CDER and CBER for drugs and biologics
- Well-understood designs
  - Group sequential design
  - Sample size re-estimation with blinded interim analysis
- Less well-understood designs
  - Adaptive dose-selection, sample size re-estimation with unblinded interim analysis, adaptive randomization, adaptive population, endpoint selection, ...

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Challenges

- Requirements of pre-specified vs. unplanned adaptations
- Timing of interim analysis vs. patient accrual
- Time and efforts in designing a complex adaptive design

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Operations

- Early interaction with FDA
- Extensive simulation studies for evaluation
- Documentation in protocol and SAP
- Available software and/or packages

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Summary

- Not intended for adaptations due to poor planning in design stage
- Improves efficiency when used appropriately
- Currently more acceptable in early-phase drug development when information is limited
- Important to communicate with clinical colleagues and FDA

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References

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- Chang (2008) *Adaptive Design Theory and Implementation using SAS and R*, Chapman & Hall
- Mehta and Pocock (2009) *Adaptive increase in sample size when interim results are promising: a practical guide with examples*, Stat in Medicine
- FDA draft guidance (2010) *Adaptive design clinical trials for drugs and biologics*
- Anderson (2014) R package *gsDesign: Group Sequential Design*

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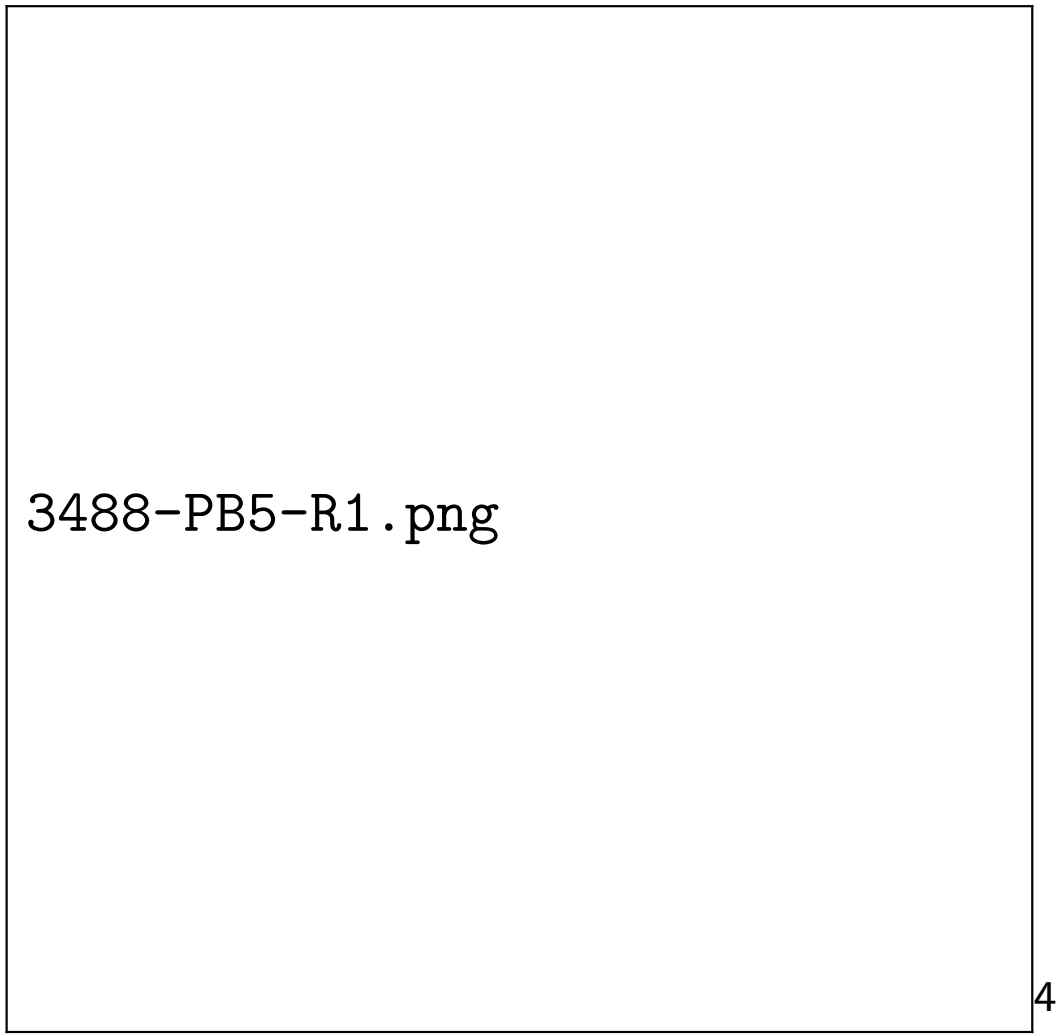
Adaptive Dose-Finding Design



[4]

[4] Figure 3. of Braun (2014) Chinese Clinical Oncology

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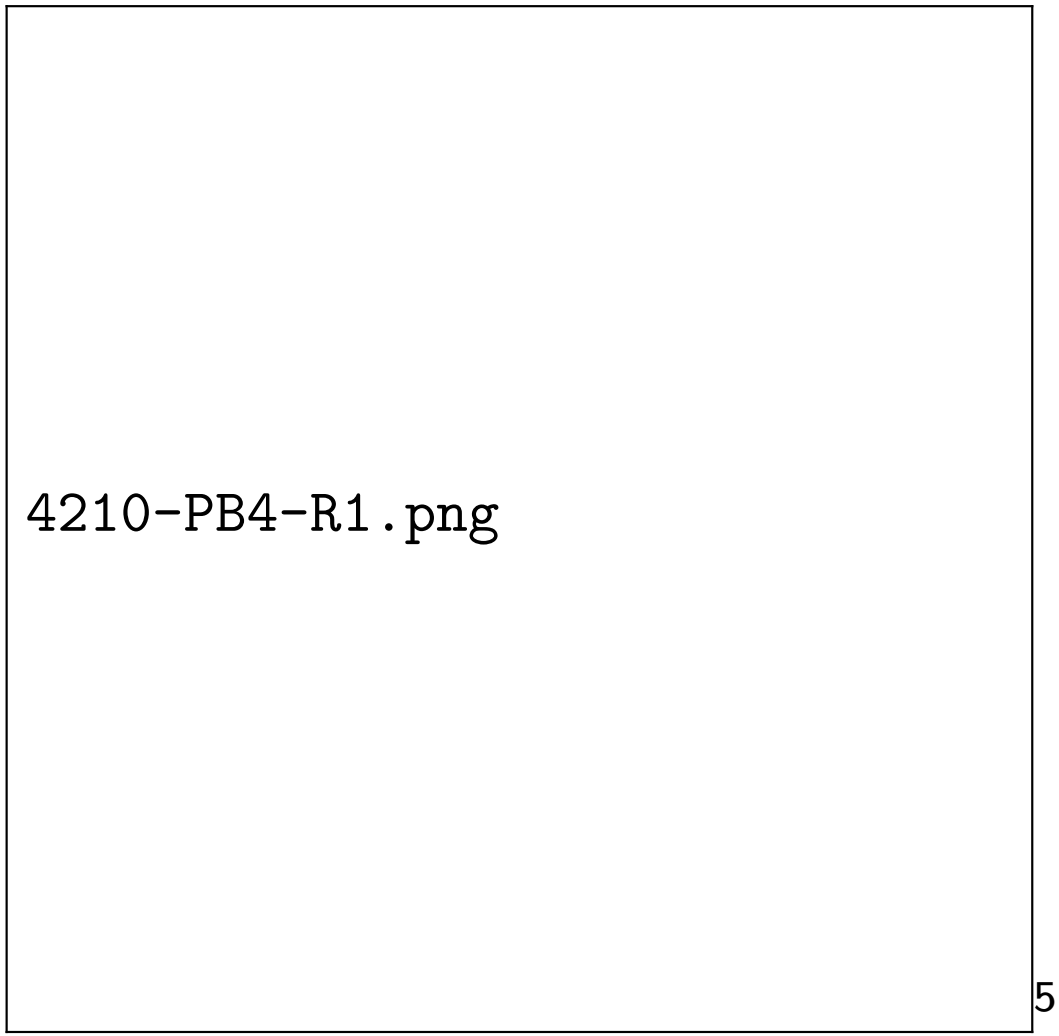
Adaptive Randomization Design



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[5]Figure 2. of Zang (2014) Chinese Clinical Oncology

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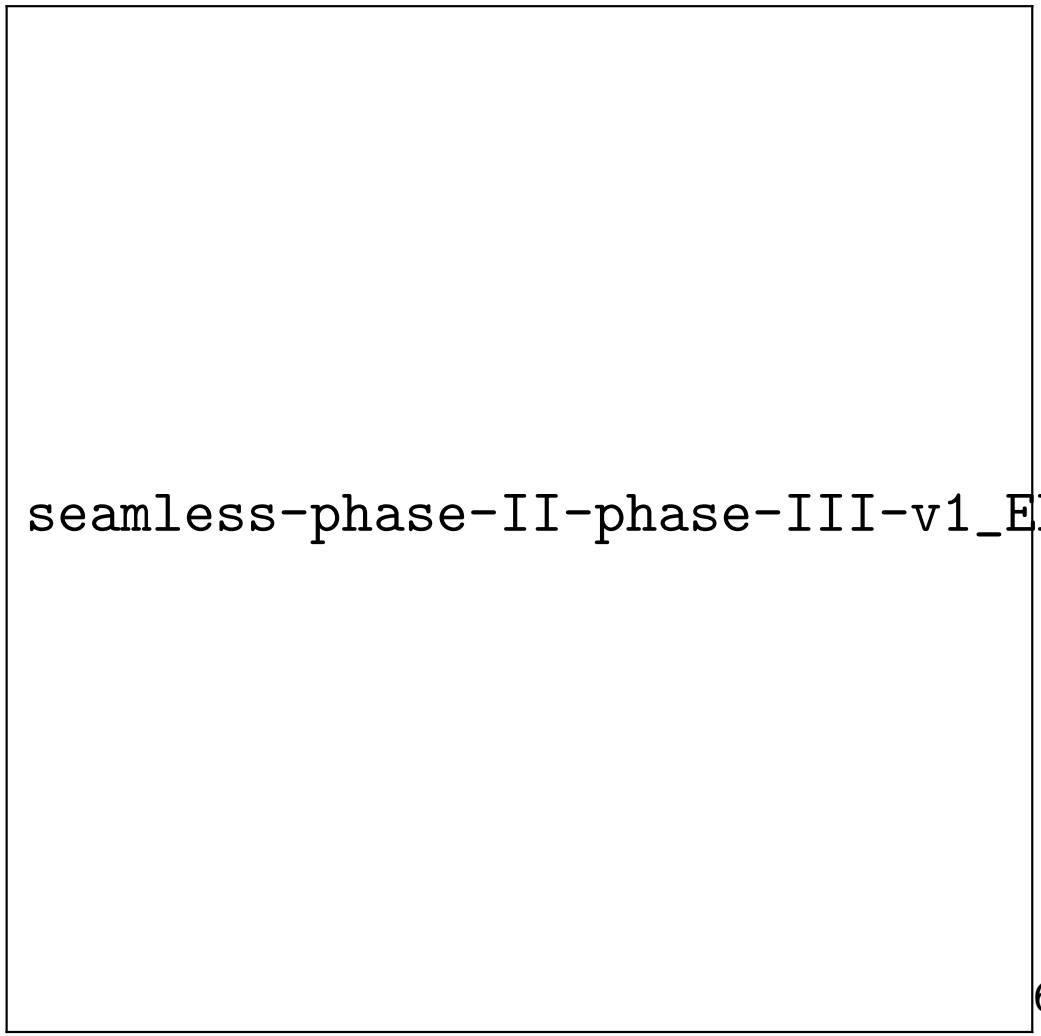
Drop-Loser Design



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[6] Figure 3. of EUPATI (2015)

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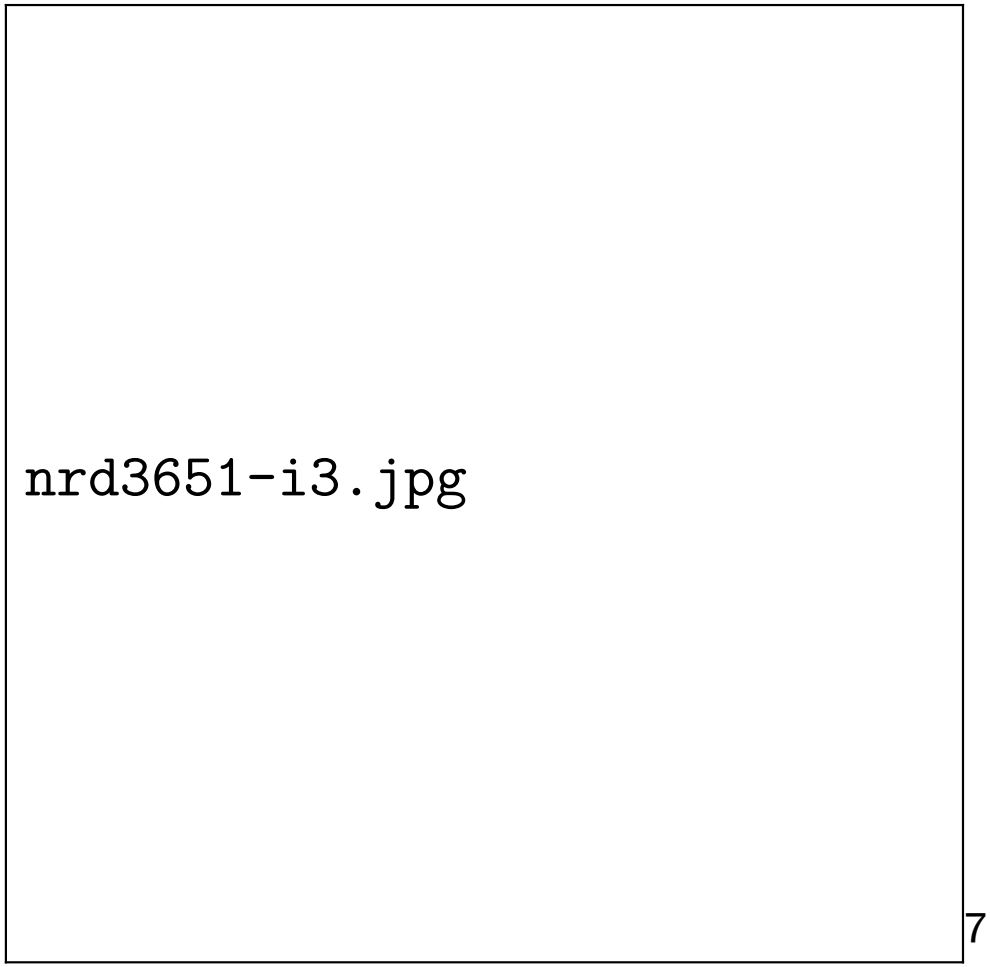
Biomarker-Adaptive Design



[7]

[7] Figure 5. of Kelloff (2012)

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Bayesian Design

beyond-traditional-designs-in-early-drug-development-5-728

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