Biostatistics 279: Intro and Optimal Designs for Clinical Trials

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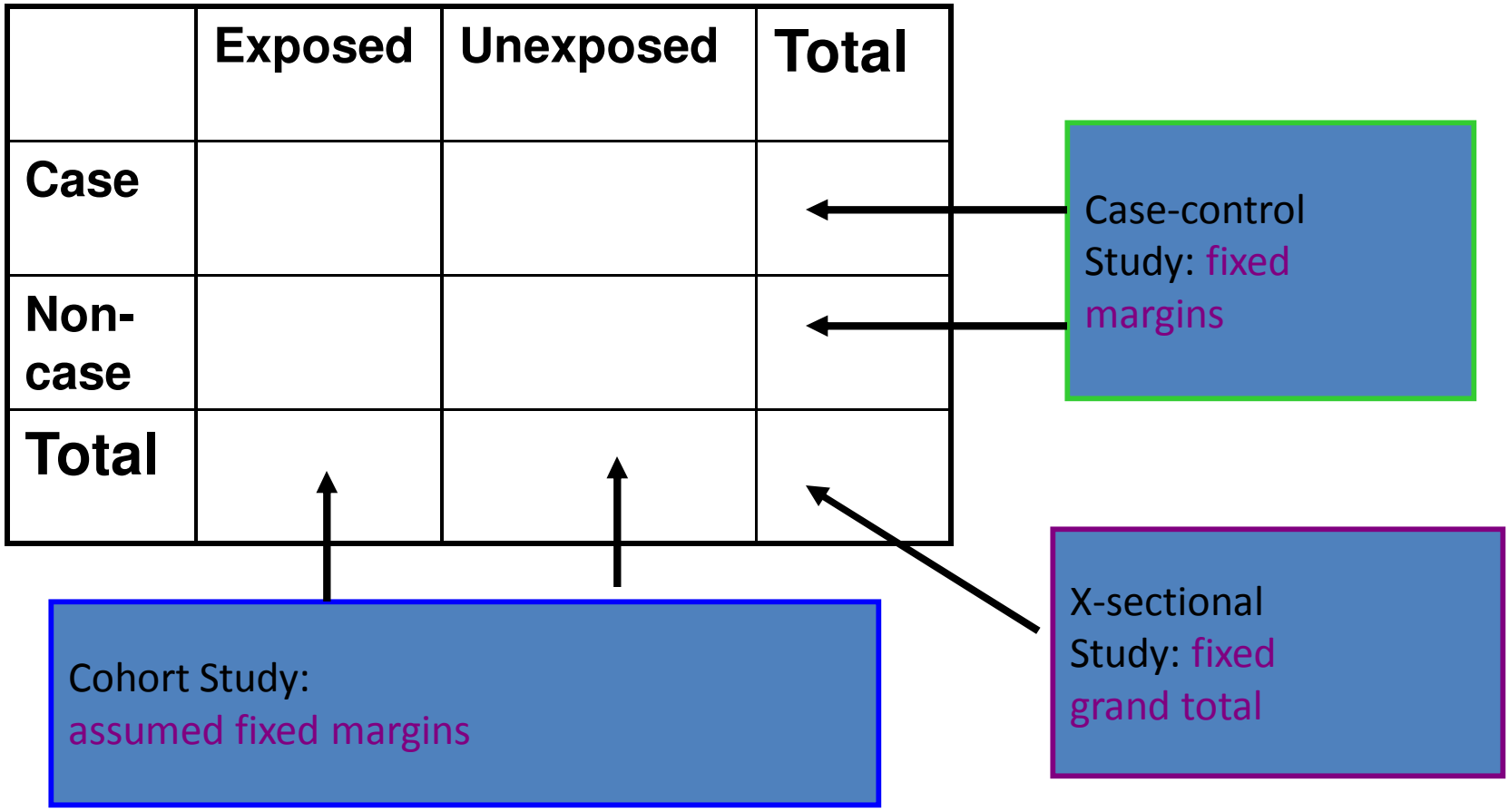
Department of Biostatistics **Fielding School of Public Health**

Outline

Observational Studies in a Picture



1 Common Studies in the Health Sciences

a Cross-Sectional Study

- Advantages
  - Fast and can be completed in a relatively time
  - Allows study of multiple potential effects of a given exposure, thereby obtaining information on potential benefits and risks
  - Able to calculate disease rates in exposed and unexposed subjects
  - Flexible choice of variables to be systematically recorded
  - Thorough quality control in measurement of study variables
- Disadvantages
  - Large numbers of subjects are required to study rare diseases
  - Potentially log duration for follow-up
  - current practice, usage, or exposure to study factors may change, making findings irrelevant
  - relatively expensive to conduct
  - control of extraneous variables may be incomplete
  - detailed study of mechanism is rarely possible

1 Common Studies in the Health Sciences (cont'd)

b Cohort study (prospective study)

- Advantages
  - In principle, provides a complete description of experience after exposure, including rates of progression, staging of disease and natural history
  - Allows study of multiple potential effects of a given exposure, thereby obtaining information on potential benefits and risks
  - Able to calculate disease rates in exposed and unexposed subjects
  - Flexible choice of variables to be systematically recorded
  - Thorough quality control in measurement of study variables
- Disadvantages
  - Large numbers of subjects are required to study rare diseases
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  - relatively expensive to conduct
  - control of extraneous variables may be incomplete
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1 Common Studies in the Health Sciences (cont'd)

c Case Control study (retrospective study)

- Advantages
  - Suitable for study of rare disease or those with long latency
  - Relatively quick to mount, conduct and inexpensive
  - Requires comparatively fewer subjects
  - Existing records can sometimes be used
  - No risk to subjects
  - Can study multiple potential causes of a disease
- Disadvantages
  - Relies on recall or records for information on past exposures
  - Validation of information is difficult if not impossible
  - Control of extraneous variables may be incomplete
  - Selection of an appropriate comparison group may be hard
  - Disease rates in exposed and unexposed subjects cannot be determined
  - Statistical methods tend to be unfamiliar to medical community and harder to explain
  - Detailed study of mechanism is rarely possible

1 Common Studies in the Health Sciences (cont'd)

d Other Types of Designs

- ad-hoc designs

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- observational studies

2 Clinical Trials

- A clinical trial is a research study to answer specific questions about a new medical treatment (medicine/drug, medical device, new therapies, vaccines), or new ways of using known treatments. Clinical trials are used to determine whether such new treatments are both safe and effective or non-inferior.

- Carefully conducted clinical trials are the fastest and safest way to find treatments that work in people. A clinical trial is one of the final stages of a long and careful research process. Studies are done with patients to find out whether promising approaches to disease prevention, diagnosis, and treatment are safe and effective.

- Historical details and information on clinical trials are available at many websites from private or regulatory agencies, see for example, http://www.availclinical.com/clinical-study/clinical-trials-history/

2 Different Phases in a Clinical Trial

- Phase I Trials: These first studies in people evaluate how a new drug should be given, how often, and what dose is safe. A phase I trial usually enrolls only a small number of patients, sometimes as few as a dozen.

- Phase II Trials: A phase II trial continues to test the safety of the drug, and begins to evaluate how well the new drug works.

- Phase III Trials: These studies test a new drug, a new combination of drugs, or a new surgical procedure in comparison to the current standard. A participant will usually be assigned to the standard group or the new group at random. Phase III trials often enroll large numbers of people.

2 Phases of Clinical Trials (cont'd)

- Phase IV Trials: These trials typically continue to investigate a drug after its initial approval from the regulatory authorities. In this phase the focus is on further evaluation of the use for which approval was secured, for comparison to or combination with other established drugs and to generate more data on safety under broader use. Phase IV trials are an important tool to strengthen the understanding of the drug and to give guidance to prescribers and patients on the safe and appropriate use under various clinical conditions.

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- The site http://www.ich.org/ for the International Conference on Harmonization (ICH) provides important guidelines to standardize technical requirements for registering medical products

Need for a RCT

[1]Foulds,GA (1958). Clinical research in psychiatry. J. Ment. Sci., 104, 259-265.

[2]Grace,ND et al. (1966). The present status of portal hypertension in cirrhosis.Gastroenterology, 50, 684-691.

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- Grace[2] (1996) reviewed 53 studies of portacaval shunt operation for portal hypertension; 75% of the 32 uncontrolled trials were strongly positive; 0% of the 6 well-controlled trials reported strongly positive results - 3 moderately positive

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- What kind of basic, animal, or clinical research information is needed to address the question?
- Are there existing databases that can be used to address the question?
- What is already known about the issue? A Bayesian study design?

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- What statistical analysis will be used to test the primary hypothesis, and how will the data be presented to convey the results (to clinicians)?
- Given the study design, the primary outcome, the postulated effect size, inherent variability (or control proportion rate), along with the statistical analysis plan, what sample size is needed?

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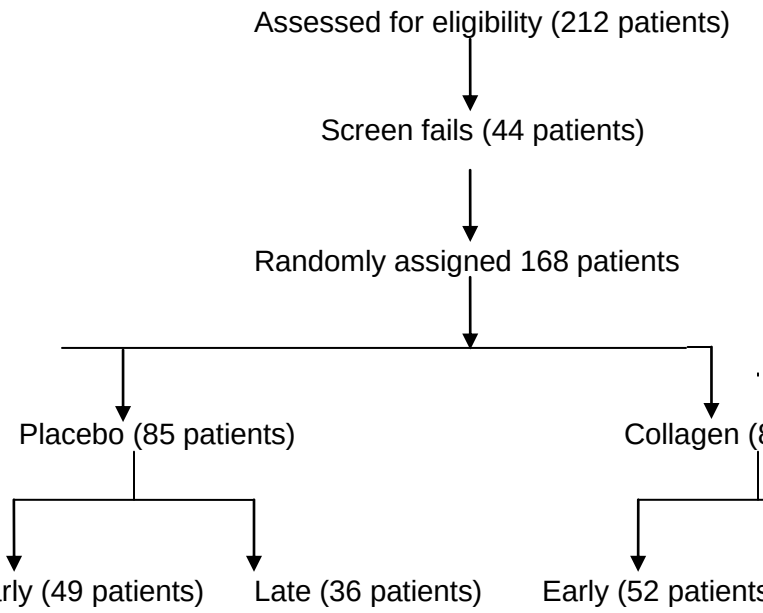
- May be used to summarize controlled RCT results, including dropouts, adverse events/severe adverse events
- Here are some examples:

BOVINE COLLAGEN TRIAL



Dropouts	16	7	21	11	55
Disease progression	5	2	8	6	21
Protocol deviation	1	1	0	0	2
Withdrew consent	3	0	2	0	5
Non-compliance	1	1	2	3	7
Death	5	1	5	1	12
Lost to follow up	1	1	3	0	5
Pregnancy	0	1	0	0	1
Beef allergy	0	0	1	0	1
Developed Inflammatory Myositis	0	0	0	1	1
MRSS data at 12 months					
Available data	39	34	41	25	139
ITT	49	36	52	31	168
Modified ITT	37	34	38	26	135
MRSS data at 15 months					
Available data	33	30	27	20	110
ITT	49	36	52	31	168
Modified ITT	37	34	38	26	135

"Available data" are from patients with baseline and 12 or 15-month data, including dropouts who returned for the 12 or 15-month visit.

"ITT" – intention to treat approach where last observations are carried forward to the 12 or 15-month visit.

"Modified ITT" – same as "ITT" except for include patients who are in the trial for at least 6 months

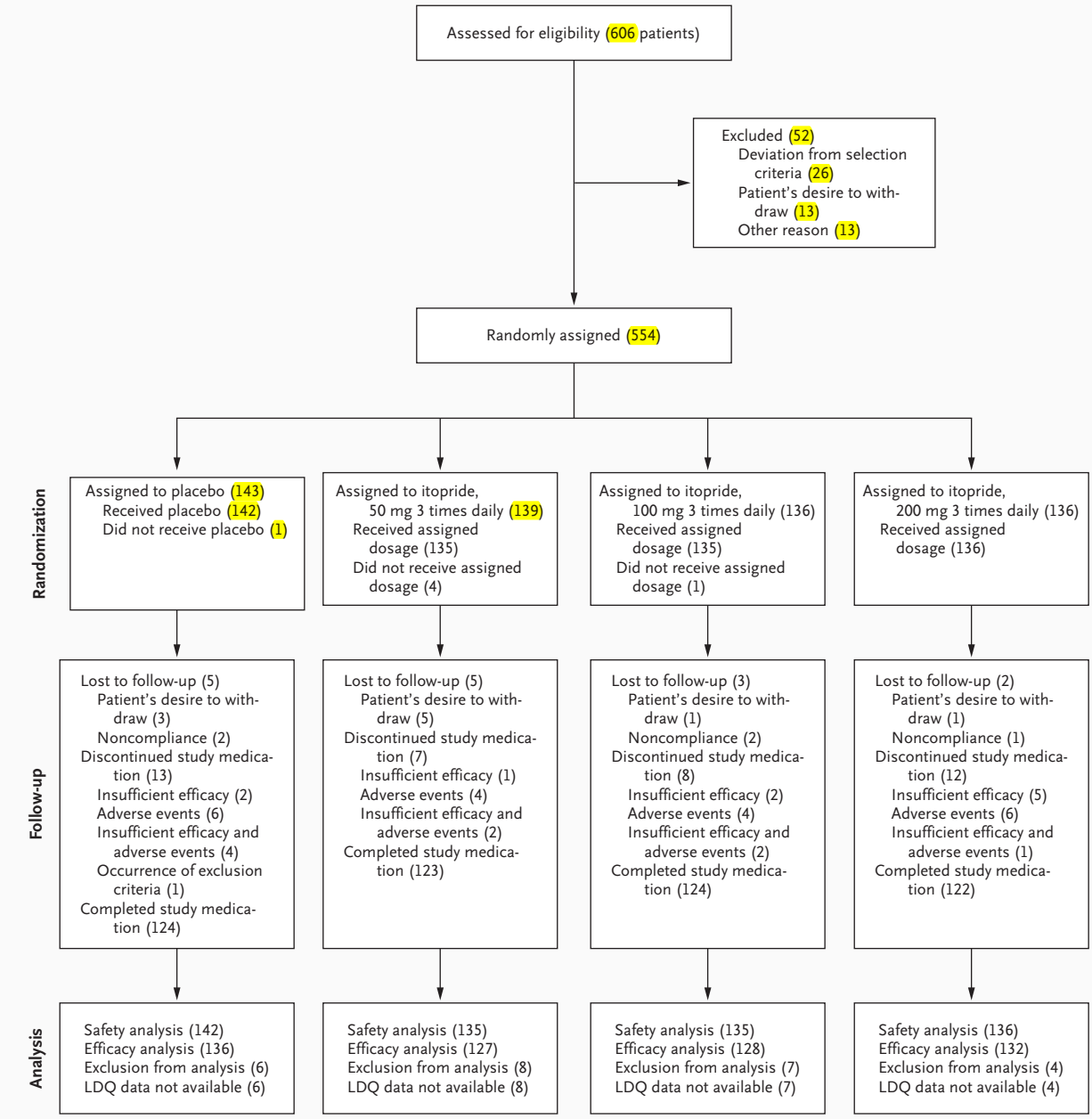
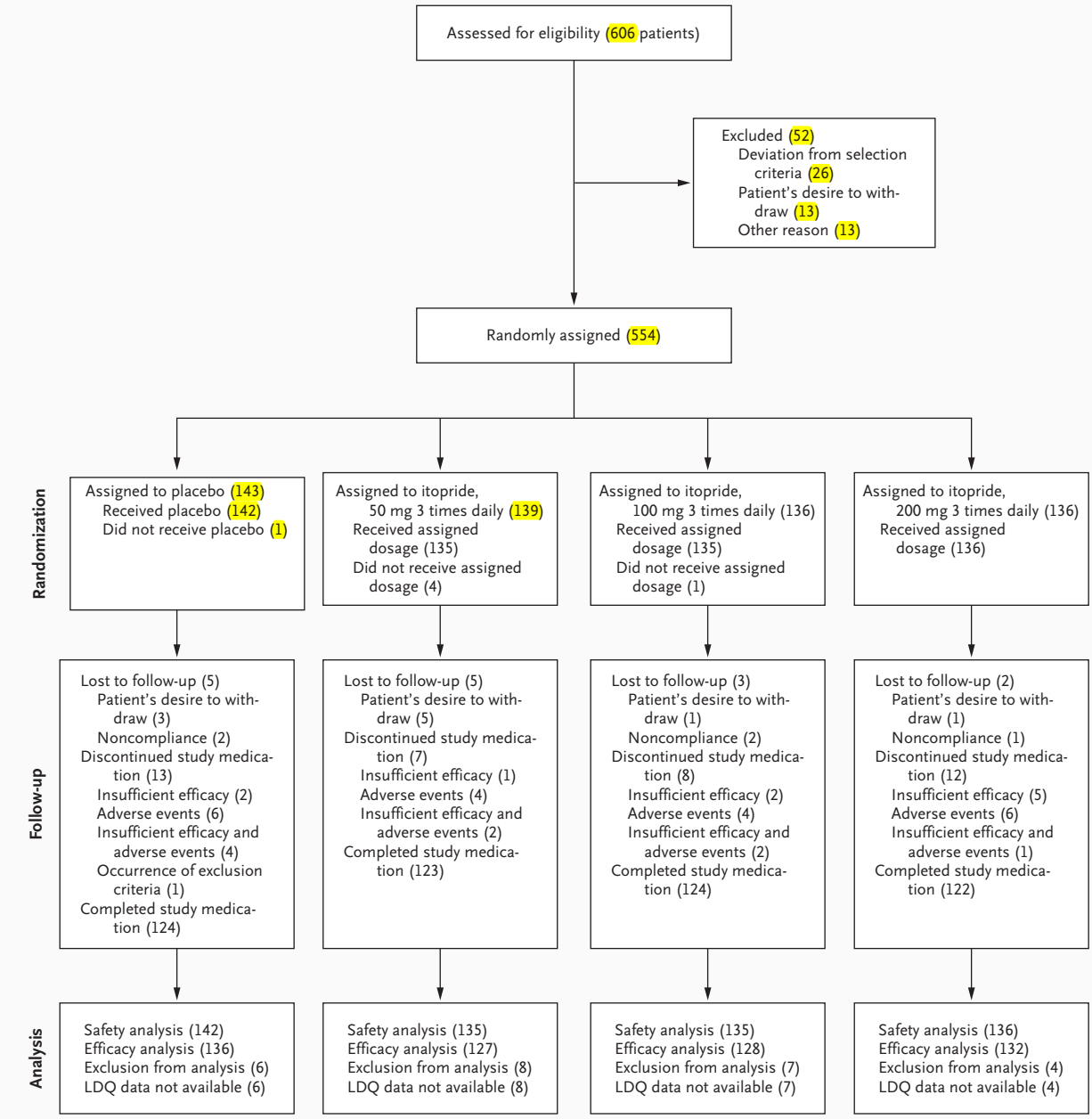


Figure 1. Enrollment, Randomization, Follow-up, and Analysis.
LDQ denotes the Leeds Dyspepsia Questionnaire.



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4 Adaptive Design Strategies

- Adaptive designs: response adaptive, covariate-adaptive
- Different types of adaptive strategies: continual monitoring or sequential determination
- Different criteria give rise to different optimal strategies

1 One Motivating Example.

Example 1. HIV transmission. Connor et al. (1994, The New England Journal of Medicine) report a clinical trial to evaluate the drug AZT in reducing the risk of maternal-infant HIV transmission.

50-50 randomization scheme is used:

- AZT Group—239 pregnant women (**20 HIV positive infants**).
- placebo group—238 pregnant women (**60 HIV positive infants**).

Given the seriousness of the outcome of this study, it is reasonable to argue that 50-50 allocation was **unethical**. As accruing information favoring (albeit, not conclusively) the AZT treatment became available, allocation probabilities should have been **shifted from 50-50 allocation proportional to weight of evidence for AZT**. Designs which attempt to do this are called *Response-Adaptive designs (Response-Adaptive Randomization).*

If the treatment assignments had been done with the **randomized play the winner rule (RPW rule)** (Zelen 1969, JASA, Wei and Durham,1978, JASA):

- AZT Group— 360 patients
- placebo group—117 patients

then, only **60 (instead of 80)** infants would be HIV positive.

Example 2 (ECMO Trial). Extracorporeal membrane oxygenation (ECMO) is an external system for oxygenating the blood based on techniques used in cardiopulmonary bypass technology developed for cariac surgery. In the literature, there are three well-document clinical trials on evaluating the clinical effectiveness of ECMO:
(i) the Michigan ECMO study (Bartlett, *et al.* 1985);
(ii) the Boston ECMO study (Ware, 1989);
(iii) the UK ECMO trial (UK Collaborative ECMO Trials Group, 1996).

The UK ECMO trial:

50-50 randomization scheme is used:

- ECMO Group—93 infants (**28 deaths**).
- Conventional group—92 infants (**54 deaths**).

If ERADE (Hu, Zhang and He, 2007) is used, then

- ECMO Group—121 infants (**36 deaths**).
- Conventional group—64 infants (**38 deaths**).

2 Overview of the Problem.

Clinical Trials: Complex with multiple (competitive) objectives

- maximizing power to detect clinically relevant difference;
- minimizing the expected total number of failures;
- maximizing the individual patient's experience in the trial;
- minimizing total monetary cost of trial;
- etc.

Randomized designs should be used to remove the potential bias in clinical trial.

Example 3. Binary response: treatment A and B.

- p_A: $P(success|A)$, $q_A = 1 - p_A$;
- p_B: $P(success|B)$, $q_B = 1 - p_B$;
- n_A: number of patients on A;
- n_B: number of patients on B, $n = n_A + n_B$.

Some important functions:

1. An objective function, $\phi(n_A, n_B)$, power or noncentral parameter;
2. Sample size $n_A + n_B$ or total number of failures $q_A n_A + q_B n_B$;
3. Allocation proportion to treatment A, $\rho(p_A, p_B) \sim n_A/n$;

Approach 1:
With fixed $\phi(n_A, n_B)$, to minimizing sample size, $n = n_A + n_B$, the solution is called *Neyman allocation*:

$$\rho(p_A, p_B) = \frac{\sqrt{p_A q_A}}{\sqrt{p_A q_A} + \sqrt{p_B q_B}}.$$

Approach 2:
With fixed $\phi(n_A, n_B)$, to minimizing total number of failures, $q_A n_A + q_B n_B$, the solution is called *optimal allocation* (see Rosenberger et al. (2001, biometrics)):

$$\rho(p_A, p_B) = \frac{\sqrt{p_A}}{\sqrt{p_A} + \sqrt{p_B}}.$$

Tymofyeyev, Rosenberger and Hu (2007, JASA) propose a general framework to find optimal ρ.

Usually $\rho(p_A, p_B)$ depends on **unknown** parameters, how to implement these optimal allocations?

Solution: Response-Adaptive Randomization can be applied to achieve above objectives.

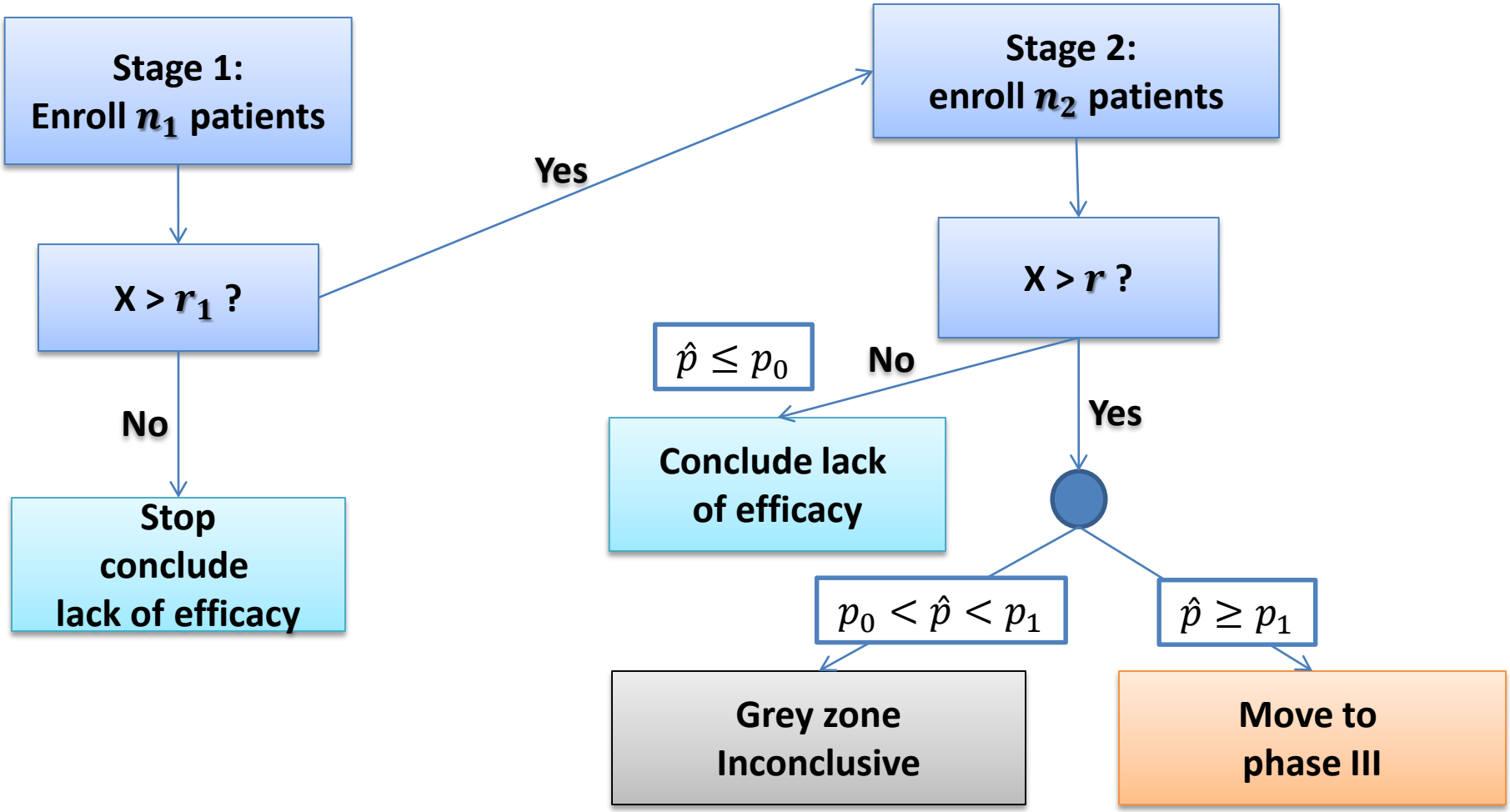
Three-step approach:

1. Find the optimal allocation;
2. Use sequential estimation, substituting estimates from the data accrued thus far into the optimal allocation;
3. Find an appropriate randomization procedure that will result in optimal allocation.

We call the resulting randomization procedure a *response-adaptive randomization procedure*, because the probability of assignment to treatments will depend on previous patient responses.

Simon's Two-Stage Designs

- X: the number of responders



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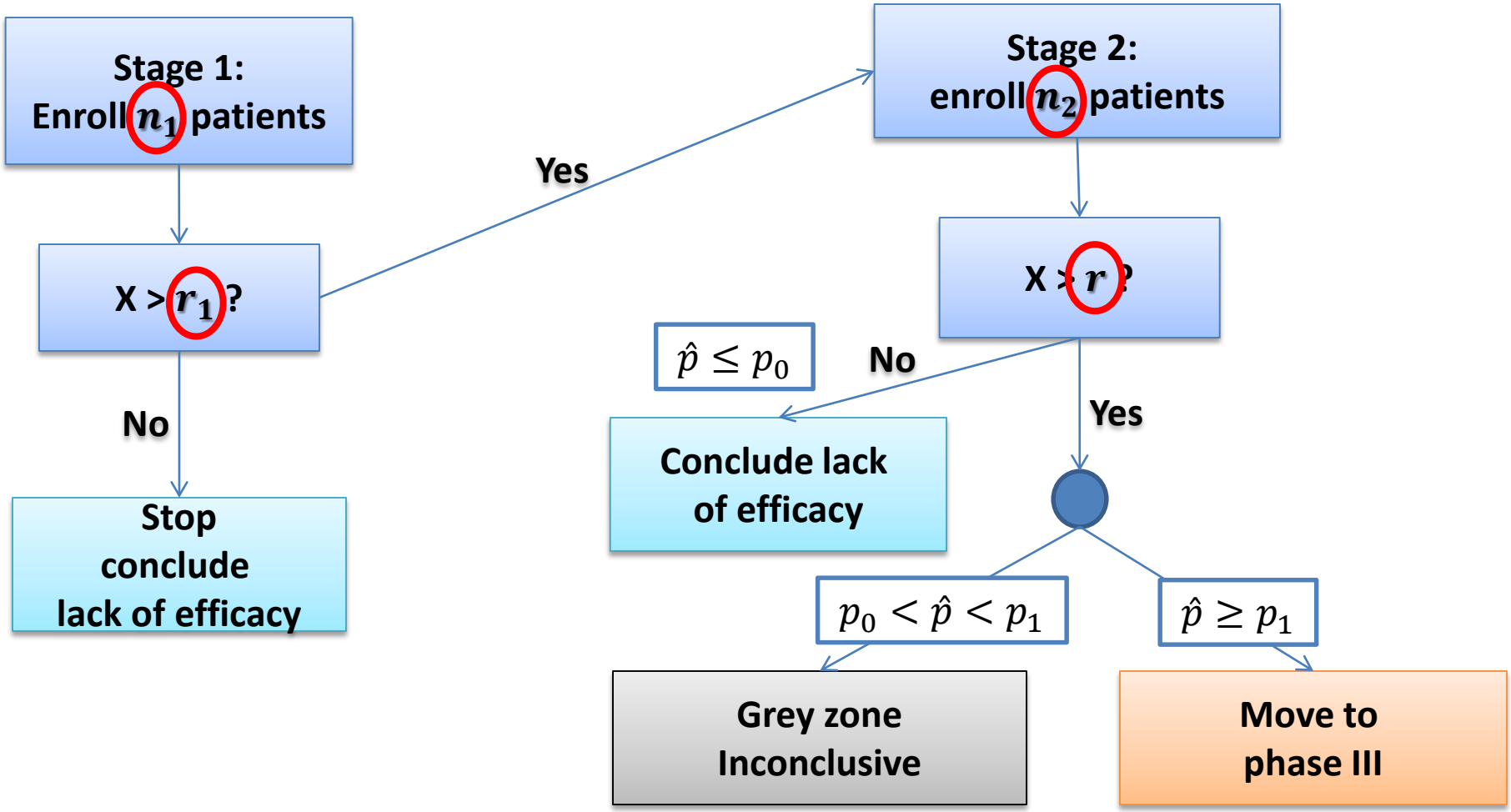
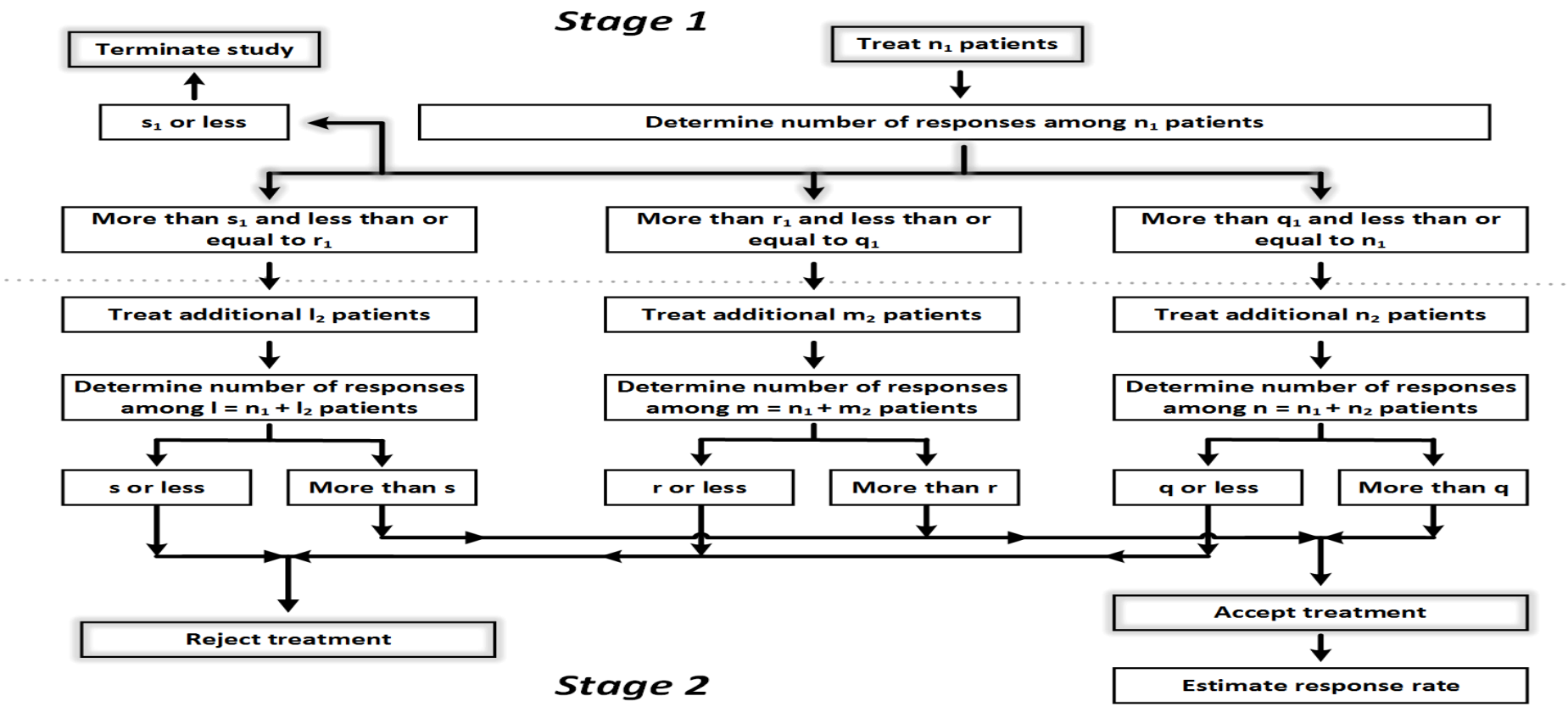


3.12 Extended 2-stage Adaptive Designs for Phase II Trials (Kim and Wong, 2016)



3.13 10 Parameters to Optimize in this problem

Problem is to optimize $\theta^T = (s_1, r_1, q_1, n_1, s, l, r, m, q, n)$ given error rates and the stipulated 3 response rates.

The parameters l, m, n are the total number of patients required for the entire trial corresponding to the alternative hypotheses, H_{11}: $p > p_1$, H_{12}: $p > p_2$, and H_{13}: $p > p_3$, respectively.

If true response probability is p, probability of failing to reject H_0 is

$$G(\theta|p) = B(s_1, n_1, p) + \sum_{x=s_1+1}^{\min(r_1,s)} b(x, n_1, p)B(s-x, l_2, p) + \sum_{x=r_1+1}^{\min(q_1,r)} b(x, n_1, p)B(r-x, m_2, p) + \sum_{x=q_1+1}^{\min(q,n_1)} b(x, n_1, p)B(q-x, n_2, p),$$

where $l = l_1 + l_2$, $m = m_1 + m_2$ and $n = n_1 + n_2$.

3.14 Minimize expected sample size and sample size

If true probability response rate is p, the expected sample size is

$$E(N|p,\theta) = n_1 + \Big(B(r_1, n_1, p) - B(s_1, n_1, p)\Big) l_2$$

$$+ \Big(\mathrm{B}(\mathrm{q}_1, n_1, p) - B(r_1, n_1, p)\Big) m_2 + \Big(1 - B(q_1, n_1, p)\Big) n_2.$$

Original Simon's design has 2 stages with 4 parameters and he proposed finding optimal design to minimize the expected sample size, or minimax optimal design that minimizes the sample size for the whole trial.

3.15 Optimality Criteria

Find $\hat{\theta} \in \widetilde{\Theta}$ for θ that satisfies 4 error constraints

$$G(\theta|p_0) \geq 1-\alpha,\ G(\theta|p_1) \leq \beta_1,\ G(\theta|p_2) \leq \beta_2 \text{ and } G(\theta|p_3) \leq \beta_3.$$

The goodness of $\hat{\theta}$ may be judged by one of these optimality criteria:

- C1: $\hat{\theta} = \arg\min_{\theta \in \widetilde{\Theta}} E(N|p_0, \theta)$;
- C2: $\hat{\theta} = \arg\min_{\theta \in \widetilde{\Theta}} E(N|p_0, \theta)$ and $\hat{\theta} = \arg\min_{\theta \in \widetilde{\Theta}} \{\max(l, m, n)\}$;
- C3: $\hat{\theta} = \arg\min_{\theta \in \widetilde{\Theta}} \{\max_{i=0,1,2} E(N|p_i, \theta)\}$;
- C4: $\hat{\theta} = \arg\min_{\theta \in \widetilde{\Theta}} \{\max_{i=0,1,2} E(N|p_i, \theta)\}$ and $\hat{\theta} = \arg\min_{\theta \in \widetilde{\Theta}} \{\max(l, m, n)\}$.

C1-C4 are extensions of Lin and Shih (2004)'s criteria and Simon's two optimality criteria are criteria C1 and C2.

3.16 Adaptive 2-stage optimal designs with 3 target responses when $\alpha = 0.05$, $\beta_1 = 0.20$, $\beta_2 = 0.10$ and $\beta_3 = 0.05$.

p_0	p_1	p_2	p_3	Optimal criteria	Method	$s_1/r_1/q_1/n_1$	s/l	r/m	q/n	$1-\alpha$	β_1	β_2	β_3	$E(N\|p_0)$	$E(N\|p_1)$	$E(N\|p_2)$	$E(N\|p_3)$	Computation time (minute)
0.05	0.20	0.25	0.30	C1	G-DPSO	0/1/4/10	3/28	3/31	5/28	0.953	0.200	0.088	0.037	17.481	27.841	29.020	29.593	5.49
					D-DPSO	0/1/2/9	4/36	3/34	3/31	0.959	0.199	0.093	0.044	18.816	30.463	31.375	31.691	5.75
				C2	G-DPSO	0/1/2/13	3/31	3/28	3/20	0.951	0.200	0.088	0.036	21.158	23.725	22.613	21.636	5.32
					D-DPSO	0/1/2/14	4/36	3/33	3/19	0.952	0.198	0.094	0.043	24.391	24.899	22.847	21.245	5.64
				C3	G-DPSO	0/2/5/11	3/28	3/28	6/21	0.956	0.200	0.084	0.033	18.330	26.458	27.042	27.f116	5.42
					D-DPSO	0/3/4/11	3/29	5/29	5/22	0.953	0.198	0.085	0.034	18.761	27.101	27.437	27.172	5.69
				C4	G-DPSO	0/1/2/15	3/28	3/27	3/24	0.958	0.198	0.077	0.026	21.698	24.904	24.615	24.354	5.3
					D-DPSO	0/1/2/14	4/32	3/30	3/22	0.960	0.198	0.079	0.028	22.675	25.189	24.130	23.260	5.66
0.55	0.70	0.75	0.80	C1	G-DPSO	15/20/21/26	48/76	29/43	23/31	0.951	0.199	0.052	0.010	41.812	63.491	60.658	51.947	41962.35
					D-DPSO	10/15/16/19	46/72	23/39	18/29	0.951	0.198	0.047	0.008	44.911	62.696	60.681	54.260	6.49
				C2	G-DPSO	17/22/23/32	47/73	32/48	24/35	0.950	0.195	0.041	0.005	51.994	54.810	46.623	39.493	41384.16
					D-DPSO	8/13/14/17	46/72	27/39	21/31	0.951	0.195	0.048	0.009	52.800	62.503	58.360	51.268	6.39
				C3	G-DPSO	15/20/21/27	46/72	27/41	24/35	0.951	0.192	0.041	0.005	44.743	59.648	54.638	46.497	41835.97
					D-DPSO	12/17/18/22	47/74	26/39	24/32	0.950	0.197	0.054	0.014	44.314	63.001	60.007	52.356	6.45
				C4	G-DPSO	17/22/23/32	47/73	32/48	24/35	0.950	0.195	0.041	0.005	51.994	54.810	46.623	39.493	41498.29
					D-DPSO	7/12/14/16	45/70	26/39	19/31	0.951	0.200	0.044	0.006	55.302	60.783	56.534	50.252	6.38

3.16 Adaptive 2-stage optimal designs with 3 target responses when $\alpha = 0.05$, $\beta_1 = 0.20$, $\beta_2 = 0.10$ and $\beta_3 = 0.05$.

p_0	p_1	p_2	p_3	Optimal criteria	Method	$s_1/r_1/q_1/n_1$	s/l	r/m	q/n	$1-\alpha$	β_1	β_2	β_3	$E(N\|p_0)$	$E(N\|p_1)$	$E(N\|p_2)$	$E(N\|p_3)$	Computation time (minute)
0.05	0.20	0.25	0.30	C1	G-DPSO	0/1/4/10	3/28	3/31	5/28	0.953	0.200	0.088	0.037	17.481	27.841	29.020	29.593	5.49
					D-DPSO	0/1/2/9	4/36	3/34	3/31	0.959	0.199	0.093	0.044	18.816	30.463	31.375	31.691	5.75
				C2	G-DPSO	0/1/2/13	3/31	3/28	3/20	0.951	0.200	0.088	0.036	21.158	23.725	22.613	21.636	5.32
					D-DPSO	0/1/2/14	4/36	3/33	3/19	0.952	0.198	0.094	0.043	24.391	24.899	22.847	21.245	5.64
				C3	G-DPSO	0/2/5/11	3/28	3/28	6/21	0.956	0.200	0.084	0.033	18.330	26.458	27.042	27.f116	5.42
					D-DPSO	0/3/4/11	3/29	5/29	5/22	0.953	0.198	0.085	0.034	18.761	27.101	27.437	27.172	5.69
				C4	G-DPSO	0/1/2/15	3/28	3/27	3/24	0.958	0.198	0.077	0.026	21.698	24.904	24.615	24.354	5.3
					D-DPSO	0/1/2/14	4/32	3/30	3/22	0.960	0.198	0.079	0.028	22.675	25.189	24.130	23.260	5.66
0.55	0.70	0.75	0.80	C1	G-DPSO	15/20/21/26	48/76	29/43	23/31	0.951	0.199	0.052	0.010	41.812	63.491	60.658	51.947	41962.35
					D-DPSO	10/15/16/19	46/72	23/39	18/29	0.951	0.198	0.047	0.008	44.911	62.696	60.681	54.260	6.49
				C2	G-DPSO	17/22/23/32	47/73	32/48	24/35	0.950	0.195	0.041	0.005	51.994	54.810	46.623	39.493	41384.16
					D-DPSO	8/13/14/17	46/72	27/39	21/31	0.951	0.195	0.048	0.009	52.800	62.503	58.360	51.268	6.39
				C3	G-DPSO	15/20/21/27	46/72	27/41	24/35	0.951	0.192	0.041	0.005	44.743	59.648	54.638	46.497	41835.97
					D-DPSO	12/17/18/22	47/74	26/39	24/32	0.950	0.197	0.054	0.014	44.314	63.001	60.007	52.356	6.45
				C4	G-DPSO	17/22/23/32	47/73	32/48	24/35	0.950	0.195	0.041	0.005	51.994	54.810	46.623	39.493	41498.29
					D-DPSO	7/12/14/16	45/70	26/39	19/31	0.951	0.200	0.044	0.006	55.302	60.783	56.534	50.252	6.38

- PSO searches over a 10-dimensional space of positive integers and finds optimal designs that a greedy algorithm cannot.

3. 17 Demonstration

Optimal Approximate and Exact Designs for the Hill's model (4 parameter logistic model)

- We present various single and multiple-objective locally optimal approximate designs for the Hill's model using different nature-inspired metaheuristic algorithms. (Cook and Wong, JASA, 1994, Song & Wong, Stat. Sinica, 1998, Huang & Wong, Biometrics, 1998, Imhof & Wong, Biometrics, 2000, Zhu, Zeng & Wong, Drug. Info Journal, 2000, Zhu & Wong, Stat. in Medicine, 2001, Hyun & Wong, Int. J. of Biostatistics, 2016)

3.18 Mean function of the Hill model

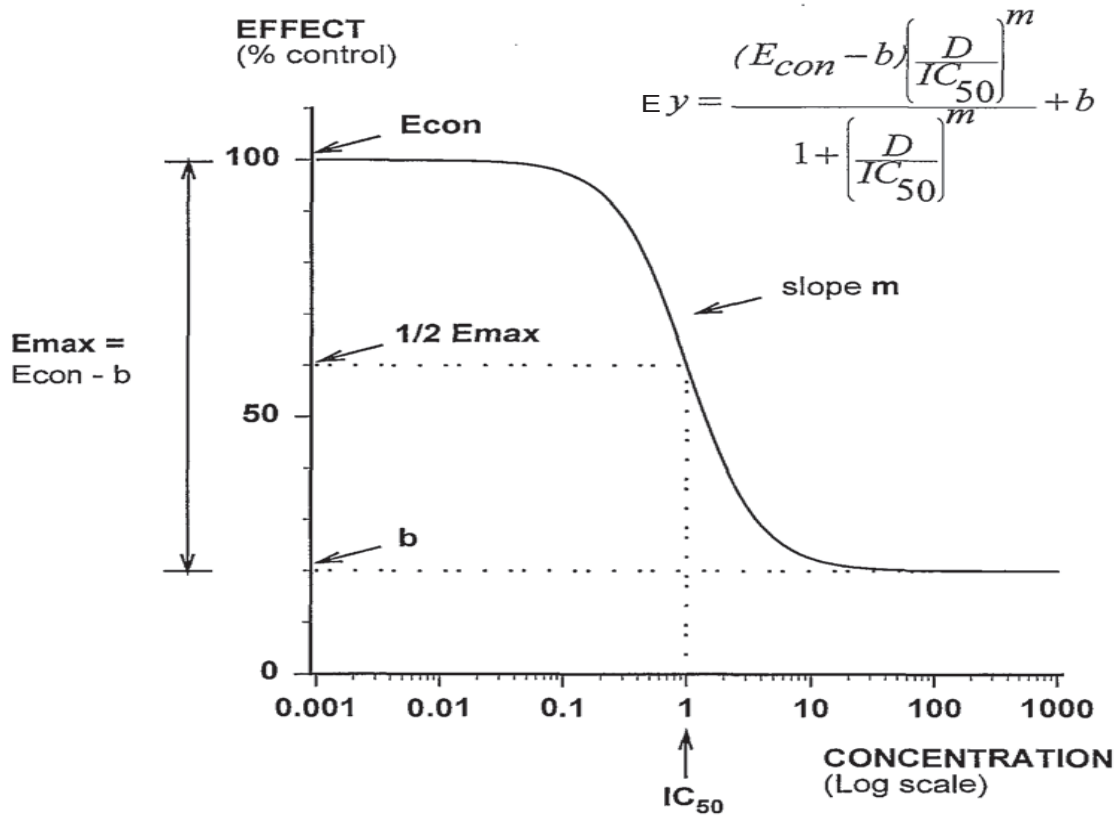
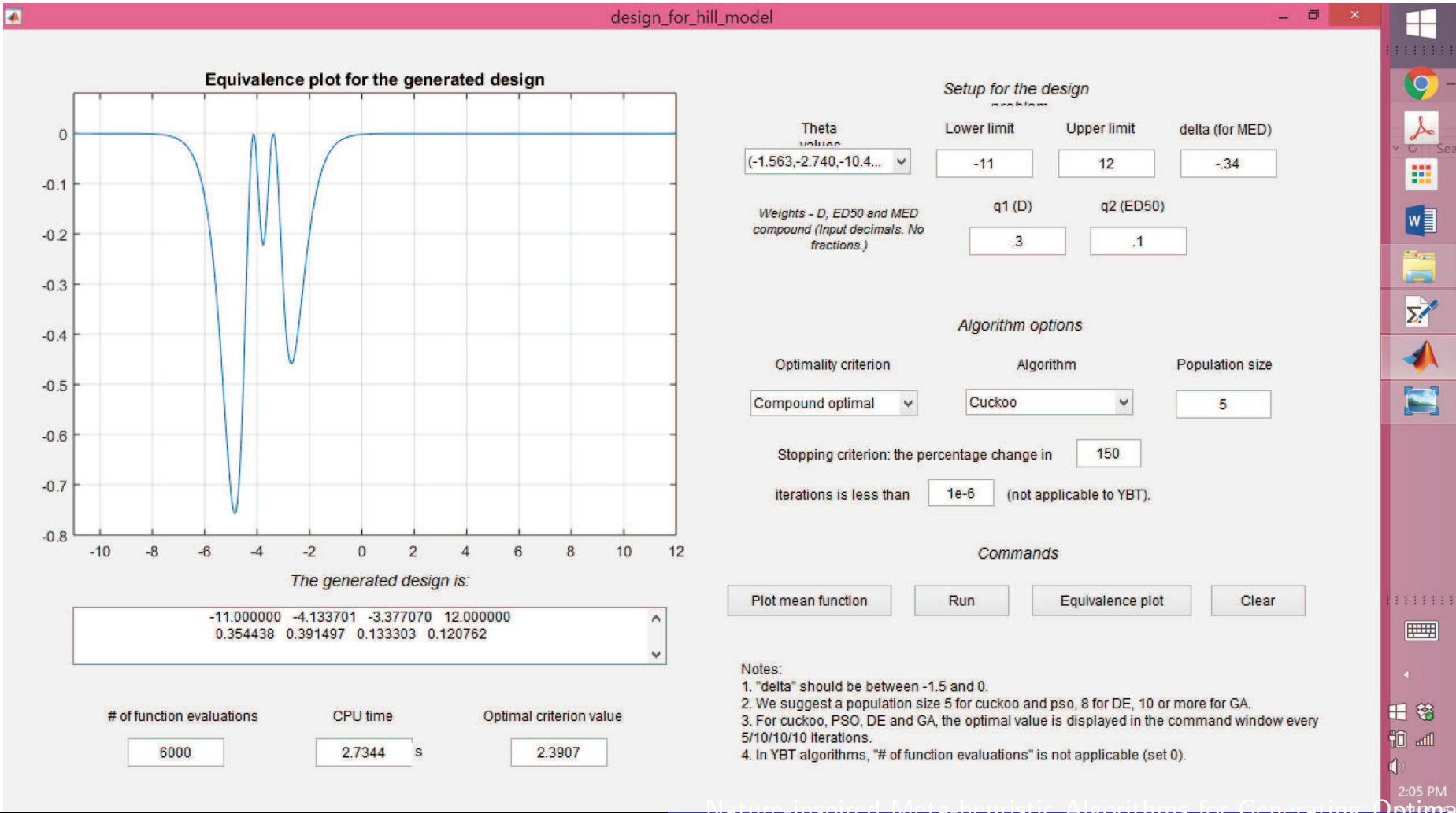


Figure 1. Graph of the 4-parameter Hill model. The following parameter values have been assumed: $E_{con} = 100$, $b = 20$, $IC_{50} = 1$, and $m = -1.5$.

3.19 Demo Display Screen



3.20 Sensitivity Plot of a Robust Multiple Objective Optimal Design