Response-adaptive designs: ethics and efficiency of estimation

Anastasia Ivanova,

Department of Biostatistics
UNC at Chapel Hill

50-50 allocation

The **randomized** clinical trial with a **50-50** allocation is regarded as the "**gold standard**" for comparing two treatments

Drawbacks of 50-50 allocation

- The principal ethical issue is that about **half of the patients** on a randomized clinical trial **receive an inferior treatment**

- 50-50 allocation is **not the most efficient**

Adaptive designs for clinical trials

1) **Stopping rules** allow to terminate a trial early with the possibility of reducing the overall number of patients in the trial
(Tsiatis and Mehta, Biometrika 2003)

2) Sample size **reestimation**

3) **Response-adaptive randomization design** seeks to skew assignment probabilities according to a certain objective, for example, to assign more patients to better treatments

AZT in Maternal-Fetal HIV Transmission

Data from Connor *et al.* "Reduction of maternal-infant transmission of HIV type 1 with zidovudine treatment" New England J Med, 1994

	Success	Failure	Total
AZT	X_1=219	Y_1=**20**	N_1=239
Placebo	X_2=178	Y_2=**60**	N_2=238
Total	T_1=397	T_2=**80**	N=477

Parameters of interest

p_1 is the probability of a success in the AZT group; $q_1 = 1 - p_1$
p_2 is the probability of a success in the placebo group; $q_2 = 1 - p_2$

$p_1 - p_2 = 0$ no difference
> 0 AZT is better

OR

odds ratio $= (p_1 \ q_2) / (q_1 \ p_2)$
$= 1$ no difference
> 1 AZT is better

Asymptotic distribution of the estimator

$$\frac{X_1}{N_1} - \frac{X_2}{N_2} \sim N(p_1 - p_2, \frac{p_1 q_1}{N_1} + \frac{p_2 q_2}{N_2}).$$

$$\log\left(\frac{X_1 Y_2}{Y_1 X_2}\right) \sim N\left(\log\left(\frac{p_1 q_2}{q_1 p_2}\right), \frac{1}{p_1 q_1 N_1} + \frac{1}{p_2 q_2 N_2}\right)$$

$$\frac{(X_1 + 0.5)(Y_2 + 0.5)}{(Y_1 + 0.5)(X_2 + 0.5)}$$

Find N_1 and N_2, $N_1 + N_2 = N$, such that the estimator has the **minimum variance**

Allocation minimizing the variance of the estimator (optimal allocation)

$p_1 - p_2$

N_1 is proportional to $\sqrt{p_1 q_1}$
N_2 is proportional to $\sqrt{p_2 q_2}$

Odds ratio

N_1 is proportional to $\sqrt{p_2 q_2}$
N_2 is proportional to $\sqrt{p_1 q_1}$

(Brittain and Schlesselman, Biometrics 1982)

Example 1

p_1=1-20/239=0.916
p_2=1-60/238=0.748

Optimal allocation for p_1 - p_2

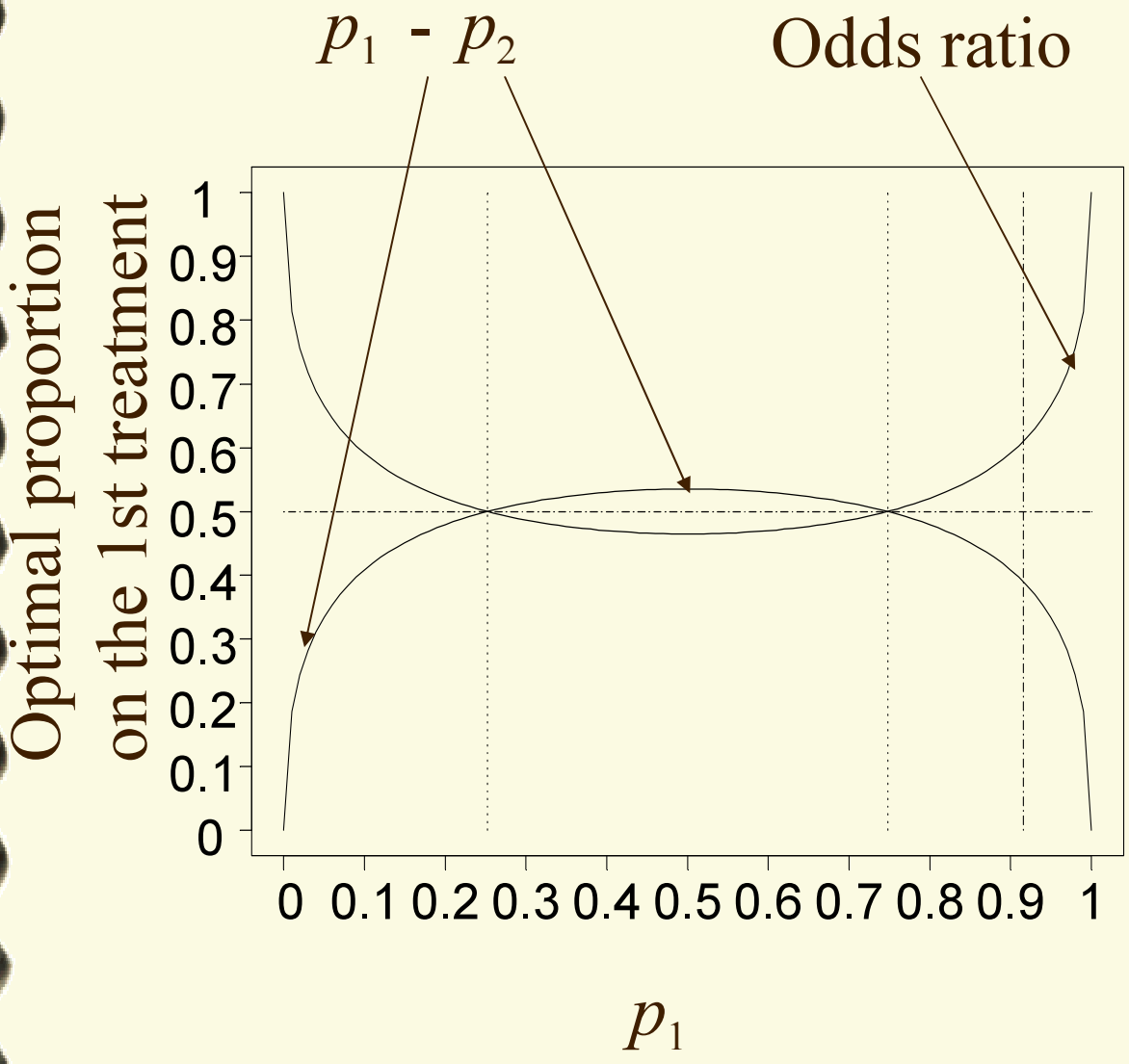
AZT placebo
39 : 61 NOT ETHICAL

Optimal allocation for odds ratio

AZT placebo
61 : 39 ETHICAL

Optimal allocation

p_2=1-60/238=0.748 is fixed



Optimal allocation for at least one of p_1 - p_2 or odds ratio is in fact ETHICAL!

When both p_1 and p_2 are greater than 0.5, optimal allocation for estimating an odds ratio is ETHICAL

When both p_1 and p_2 are small, optimal allocation for estimating p_1 - p_2 is ETHICAL

Adaptively biased coin (ABC)

Hayre and Turnbull (Biometrika, 1981), Eisele (JSPI, 1994)

1. At each stage n estimate p_1 and p_2

$$\hat{p}_{1,n}, \quad \hat{q}_{1,n} = 1 - \hat{p}_{1,n}$$
$$\hat{p}_{2,n}, \quad \hat{q}_{2,n} = 1 - \hat{p}_{2,n}$$

2. Assign the next patient to AZT with probability

$$\pi_n = \frac{\sqrt{\hat{p}_{2,n}\hat{q}_{2,n}}}{\sqrt{\hat{p}_{1,n}\hat{q}_{1,n}} + \sqrt{\hat{p}_{2,n}\hat{q}_{2,n}}}$$

to placebo w. p. 1- $\square_n$

Inverse sampling as an adaptive design

Haldane (Biometrika, 1945)
Zelen (JASA, 1969)

Assign subjects until you observe $\boldsymbol{Y}$ **failures** on each treatment:

$Y=q_1 E[N_1]$ $\quad E[N_1]=Y_1/q_1=Y/q_1$
$Y=q_2 E[N_2]$ $\quad E[N_2]=Y_2/q_2=Y/q_2$

e.g. the assignment is proportional to $\mathbf{1/q_1}$, or to $\boldsymbol{q_2}$ in the case of two treatments

Optimal allocation is proportional to

$\& \; p_2q_2 \sim \& \; \boldsymbol{q_2} \sim \sim \boldsymbol{q_2}$

Optimal : 61:39
Inverse sampling: 75:25

Example (continued)

$Y(1/q_1+1/q_2)=N$

$Y(239/20+238/60) = 477$

- $Y=30$

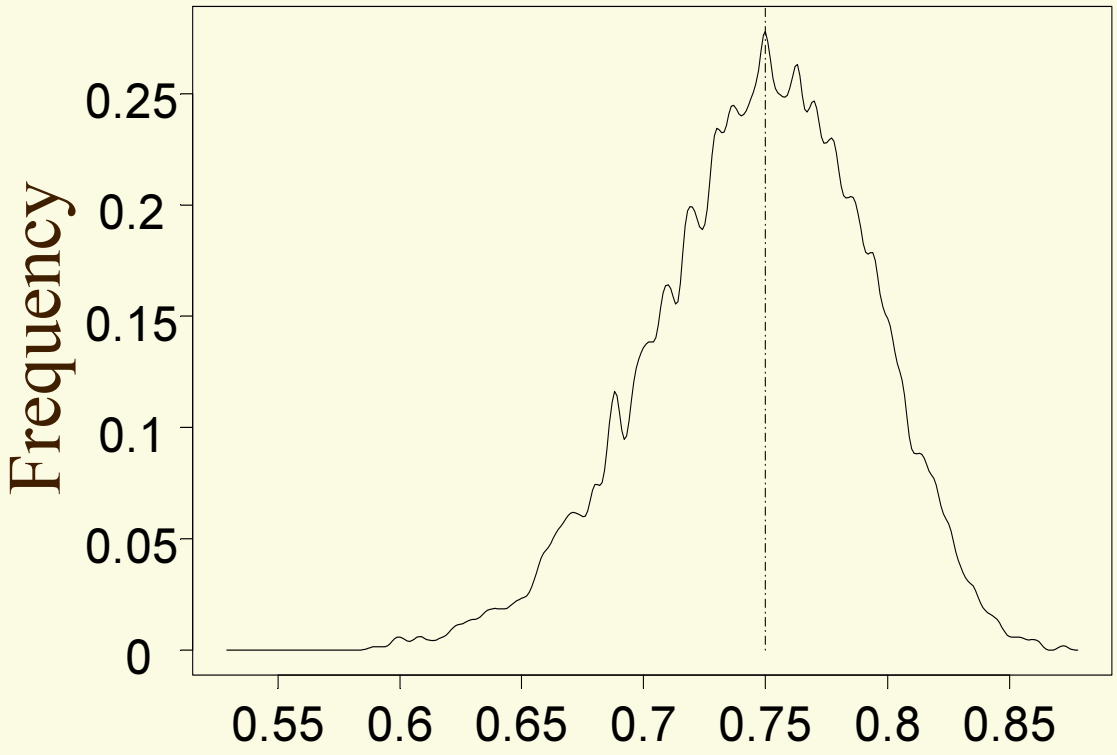
	Success	Failure	Total
AZT	$E(X_1)=328$	$Y_1=30$	$E(N_1)=358$
Placebo	$E(X_2)=89$	$Y_2=30$	$E(N_2)=119$
Total	$E(T_1)=417$	$T_2=60$	$E(N)=477$

Allocation proportion according to inverse sampling

p_1=1-20/239=0.916

p_2=1-60/238=0.748

Y=30 failures on each treatment



Proportion of subjects on AZT $\frac{N_1}{N_1+N_2}$

Urn model for inverse sampling

• Consider the urn with Y RED (AZT) and Y WHITE (placebo) balls

• When a subject comes in one ball is drawn (without replacement). If it is a RED ball the subjects receives AZT; when a WHITE ball is drawn the subject receives placebo

• If the treatment is a success the ball is returned to the urn

Limitation of the use of Inverse sampling

1. Sampling is with respect to the number of failures not trials. The **number of trials** is a **random** variable.

2. Several assignments in the end might be **deterministic** (balls of only one kind are left in the urn). This may cause selection bias.

Modified inverse sampling

Want to sample **with respect to the number of trials:** N_1 and N_2

$N_1 = Y + M_1$ RED and
$N_2 = Y + M_2$ WHITE balls

The rest is the same:

- If a RED ball is drawn the subjects receives AZT; WHITE - placebo
- If the treatment is a success the ball is returned to the urn

But…the allocation is almost a fair coin allocation since there are **a lot of balls** in the urn initially

Drop-the-loser rule (DL rule)

• Consider an urn containing **ONE** ball marked with a letter **"I" (immigration)**

• **When a ball marked with "I" is drawn, one RED and one WHITE ball are added to the urn**

The rest is the same:

• If a RED ball is drawn the subjects receives AZT; WHITE - placebo

• If the treatment is a success the ball is returned to the urn

Sample with respect to $N_1 + N_2$

Example

Initial urn composition

(R = 0, W = 0; “I” = 1)

First draw

(R = 1, W = 1; “I” = 1)

Second draw

- A RED ball is drawn
- A success is observed on AZT

(R = 1, W = 1; “I” = 1)

Third draw

- A WHITE ball is drawn
- A failure is observed on placebo

(R = 1, W = 0; “I” = 1)

Relationship between the DL rule and inverse sampling

DL is similar to inverse sampling but instead of Y and Y balls that are in the urn initially we have balls immigrating with a constant rate to replenish the urn

1. DL rule assigns proportionally to $\mathbf{1}/q_1$ and $\mathbf{1}/q_2$ in the limit (as does the inverse sampling rule)

2. DL rule **randomizes** (inverse sampling is deterministic after Y failures are observed on one of the treatments)

Comparison with the Randomized Play-the-winner rule

Play-the-winner: Zelen (JASA, 1969)

Randomized play-the-winner: Wei and Durham (JASA, 1978)

60 papers in CIS

ECMO trial (Bartlett *et al.* Pediatrics, 1985)

	Success	Failure	Total
ECMO	9	0	N_1=**9**
Control	0	1	N_2=**1**
Total	9	1	N=**10**

Randomized Play-the-winner rule

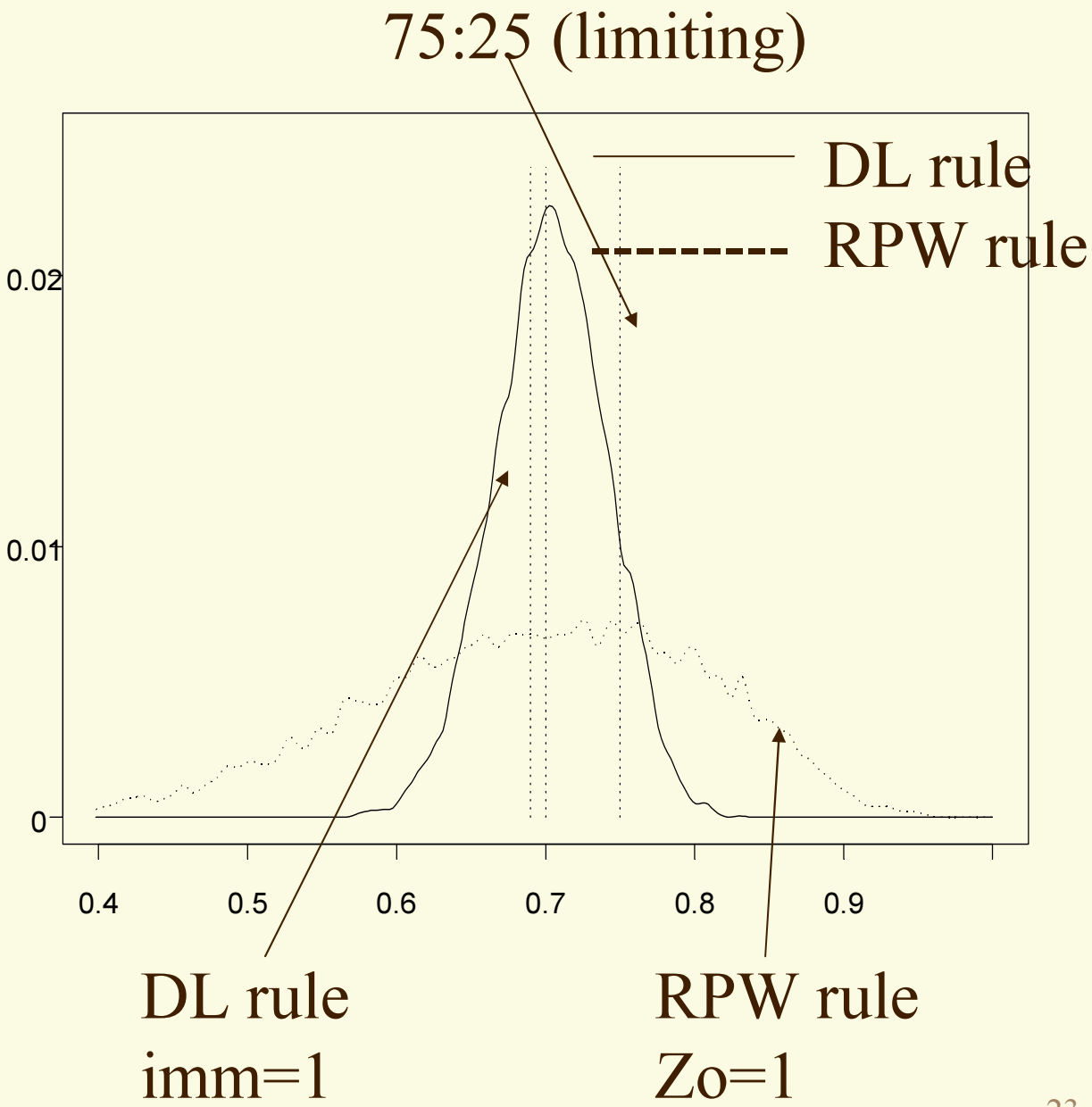
1. The RPW is an adaptive design based on the urn model for allocation:

- if a success, return the ball and **one ball of the same kind**
- if a failure, return the ball and **add one ball of the opposite kind**

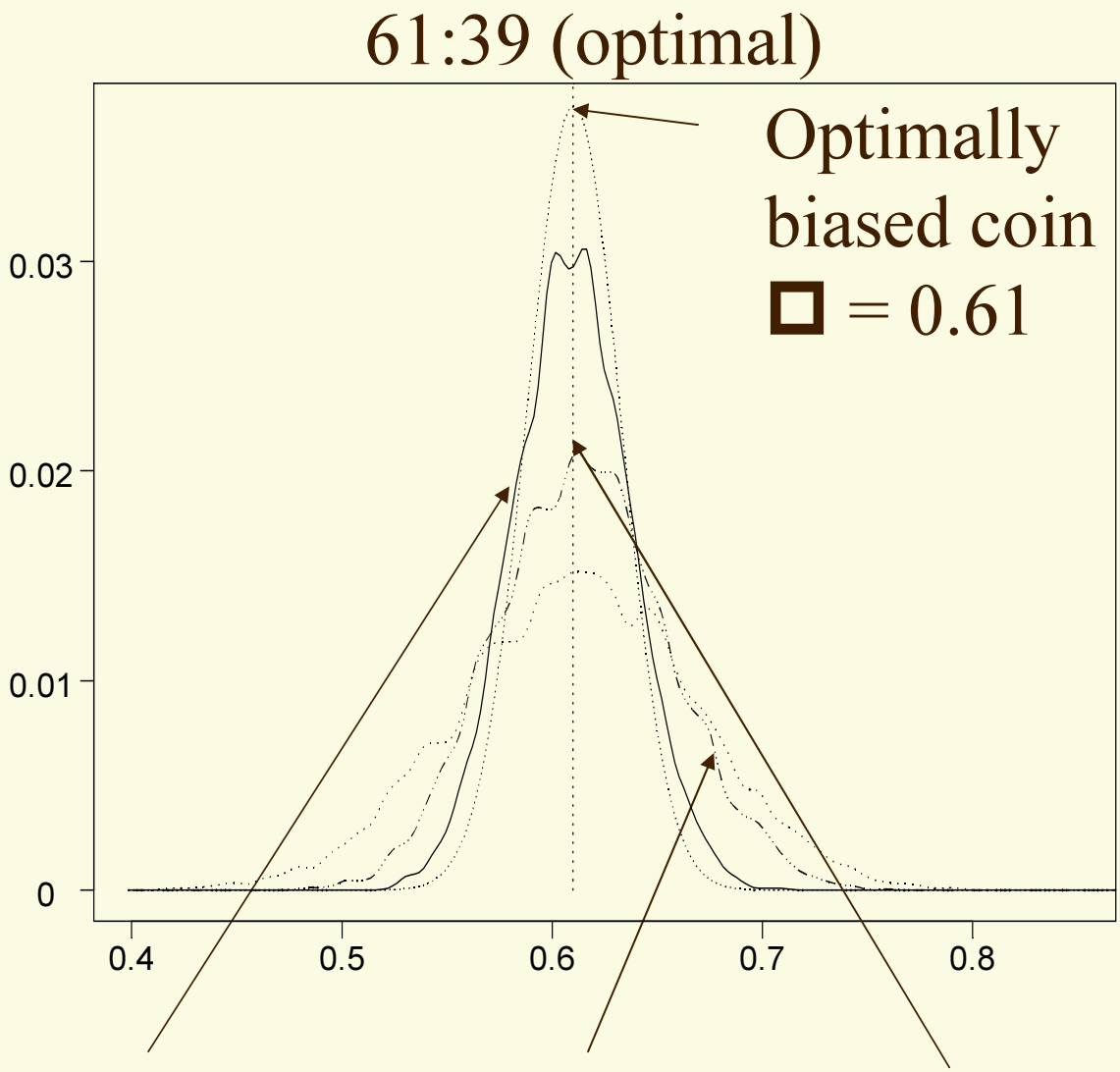
2. The RPW assigns proportionally to $\mathbf{1}/q_1$ and $\mathbf{1}/q_2$ in the limit (as does the inverse sampling rule and the DL rule)

3. The RPW **randomizes**

Distribution of the allocation proportion



Distribution of the allocation proportion



Comparison of the DL rule and the RPW

1. Both **DL** and **RPW** assign proportionally to $\mathbf{1}/q_1$ and $\mathbf{1}/q_2$ in the limit (as does **inverse sampling**)

2. Both DL and RPW **randomize** subjects

3. DL is **less variable** than RPW and hence yields more efficient estimation on average

Comparisons of MSEs of odds ratio for different designs

Allocation	Rule	MSE
$(70:30)_E$*	DL rule (I=1)	1.35
$(61:39)_E$ **	DL rule (I=7)	1.27
$(61:39)_E$ **	RPW (Z_0=19)	1.29
(61:39)**	Biased Coin (61:39)	1.21
(50:50) ***	Biased Coin (50:50)	1.32

* (70:30) with **64 failures**

** The most efficient allocation for estimating the odds ratio

(61:39) with **71 failures**

*** Equal allocation

(50:50) with **80 failures**

Comparison of DL rule and equal allocation for large p_1 and p_2

The DL rule improves power and reduces the number of failures if both p_1 and p_2 are large and the odds ratio is of interest, for example, the Fisher's exact test is used (Ivanova and Rosenberger, DIJ 2001):

p_1	p_2	power		# of failures		ssize
		DL	E	DL	E	
0.6	0.7	0.78	0.78	244	249	712
0.7	0.8	0.77	0.77	141	146	584
0.8	0.9	0.78	0.76	54	59	394
0.6	0.8	0.76	0.75	44	49	162
0.7	0.9	0.77	0.74	21	24	122
0.6	0.9	0.78	0.74	13	16	64

Comparison of DL rule and equal allocation for small p_1 and p_2

The DL rule does not improve the power in the case where p_1 and p_2 are low, p_1 - p_2 is of interest, and sample size is such that equal allocation yields 80% power (Rosenberger et al., Biometrics 2001).

Any response-adaptive design will be beneficial if the sample size is much higher than required

Conclusion

1. The Drop-the-loser rule is a very good response-adaptive randomization procedure.

2. The Drop-the-loser rule can reduce the number of failures and increase the power compared to equal allocation if both success probabilities are high and the odds ratio is of interest, for example, the Fisher's exact test is used.

Reasoning against adaptive allocations

- Response is not immediate
- "If-you-think-one's-better-then-why-randomize"?
- Use stopping rules instead
- There might be time trends in the data (patients get sicker)
- Possibility for selection bias
- Adaptive designs are so complicated they are virtually impractical

References

Ivanova, A. (2003). A Play-the-Winner-Type Urn Design with Reduced Variability. *Metrika*, **58**, 1-13.

Ivanova, A., and Rosenberger,W.F. (2001). Adaptive Designs for Clinical Trials with Highly Successful Treatments. *Drug Information Journal*, **35**, 1087-1093.

Rosenberger, W. F., Stallard, N., Ivanova, A., Harper, C., and Ricks, M. (2001). Optimal Adaptive Designs for Binary Response Trials. *Biometrics*, **57** (3), 833-837.

Challenges in obtaining distributional results

1. Can consider sampling with respect to
- "virtual" time
- number of immigrations
- total sample size

2. Obtain the results on continuous time immigration-death process (probability generating functions for trials, successes and failures)

3. Convert these in terms of the number of subjects instead of time

(Ivanova *et al*., Sankhya B 2000, 61)

Application issues

Should adaptive designs be used

- … for mild or life threatening diseases?
- …when anticipated treatment difference is large or small?
- … more frequently that they have?

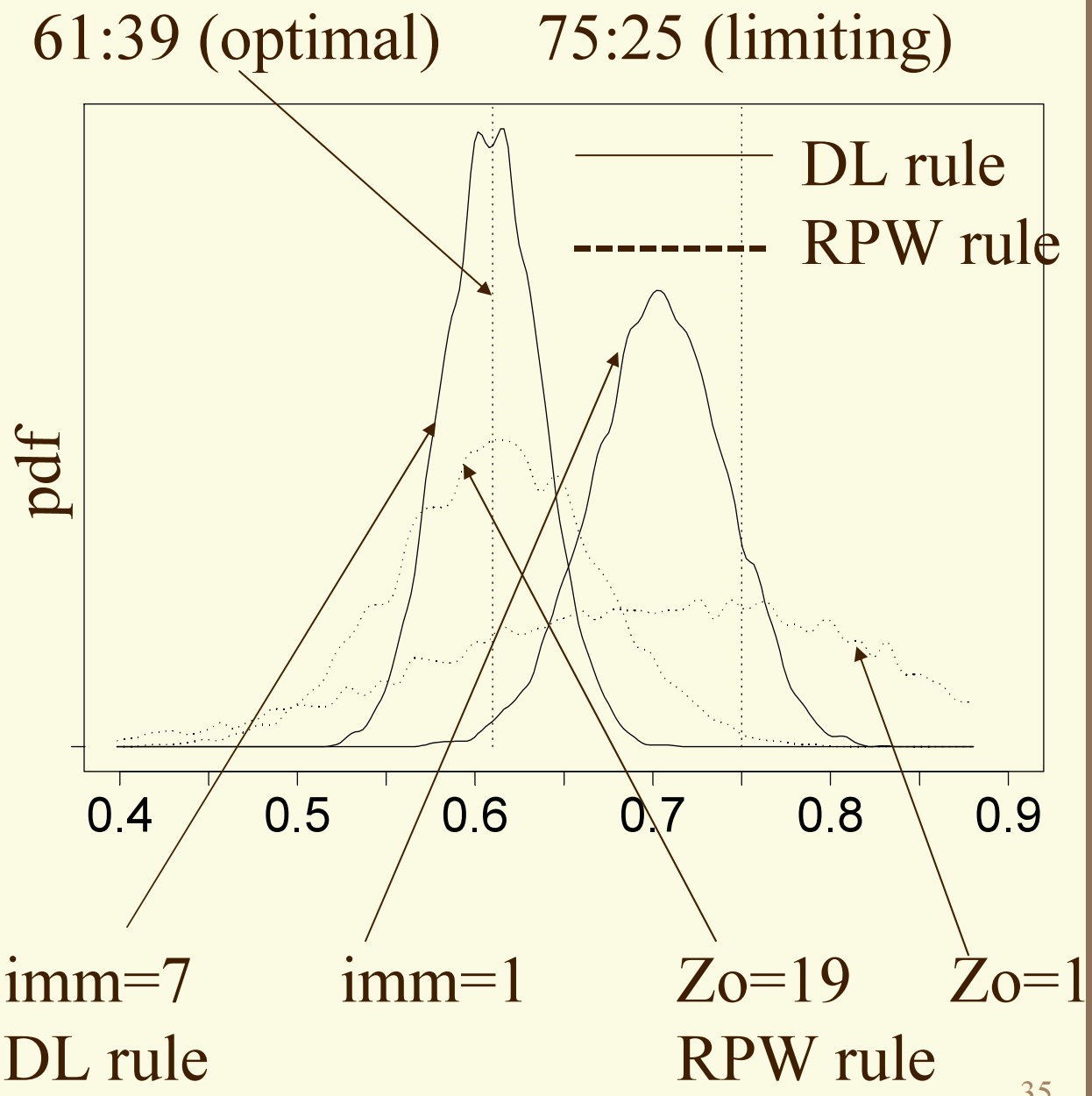
Challenges in obtaining distributional results

1. Obtain the results on continuous time immigration-death process (probability generating functions for trials, successes and failures)

2. Convert these in terms of the number of subjects instead of time

3. Since the responses are dependent have to use martingale technique to show consistency, asymptotic normality and asymptotic independence of estimators
(Ivanova *et al*., Sankhya B, 2000)

Distribution for the allocation proportion



Adaptive designs

Sequential adaptive design seeks to skew assignment probabilities to favor the treatments performing better thus far in the study, proportionately to the magnitude of the treatment effect

But...

- **high variability**
- **lost of efficiency** when allocation is skewed

Relation of the DL rule to continuous time Markov (MAPKOB) process

Relation of the DL rule to continuous time Markov
(MAPKOB) process
The DL rule is a discrete analog of a continuous time pure death process with immigration

OR

a waiting line model with infinite number of servers

The choice of parameter

Start the urn with a immigration balls (corresponds to the Poisson immigration process with rate a)

Choose a so that given probabilities of success estimated before the trial proportion of the subjects assigned to placebo is equal to the optimal

Parameters of interest

Ethical parameters

expected proportion of subjects assigned to each treatment and its variance

expected number of treatment failures

Inferential parameters

MLE of p_1 and p_2

unbiased estimates of p_1 and p_2. MLE estimate tends to underestimate pi. For example, in inverse sampling scheme X/(N-1) is unbiased

???

$N_1(t)/(N_1(t)+ N_2(t)) =$

$E(N_1(t))=at/q_1-a/q_1^2$

$E(N_2(t))=at/q_2-a/q_2^2$

$E(N_1(t)+ N_2(t)) = at(1/q_1+ 1/q_2)$
$+a(1/q_1^2+1/q_2^2)$

$E(N_1(t^*)+ N_2(t^*)) = 477$

hence $t^* =$

and

Formulae

$E(N_1(t))=at/q_1-a/q_1^2$

$E(N_2(t))=at/q_2-a/q_2^2$

$E(N_1(t)+ N_2(t)) = at(1/q_1+ 1/q_2)$
$+a(1/q_1^2+1/q_2^2)$

$E(N_1(t^*)+ N_2(t^*)) = 477$

hence $t^* =$

and $N_1(t)/(N_1(t)+ N_2(t)) =$

the urn model induces a stochastic process, the convergence properties of which allow selection of design points in s distribution that approximated the optimal designs

new methods for planning clinical trial 1) develop stopping rules so that a trial can be terminated early with the possibility of reducing the overall number of patients on a randomized clinical trial 2) methods which make use of the accruing outcome data that allow changing treatment allocation during the course of the trial. The principal idea is, during the course of the study, to allocate fewer patients to proportionally treatments which appears to be accruing less favorable endpoint information.

N balls are placed in a basket
Two fools are sitting next to it
They are taking the balls out in turns
While time *t* goes to infinity

Russian folklore

Example (continue)

The length of the 95% CI for odds ratio (based on the Normal approximation)

Inverse	(25:75)	[1.11]
optimal	(39:61)	1.06
equal	(50:50)	1.09

Total number of failures

Inverse	(25:75)	60
optimal	(39:61)	71 [Expected]
equal	(50:50)	100 [Expected]

Asymptotic distribution of the estimator

$X_1/N_1 - X_2/N_1 \sim$
$N(p_1 - p_2, p_1 q_1/N_1 + p_2 q_2/N_2)$

$N1 = piN$
$N2 = (1-pi)N$

$X_1 Y_2 / (Y_1 X_2) \sim$
$N((p_1 q_2)/(q_1 p_2),$
$\otimes 1/(p_1 N_1) + 1/(q_1 N_1) + 1/(p_2 N_2) + 1/(q_2 N_2)$
$/\otimes N$

The title is: "The Drop-the-Loser Rule in Medical Trials"

Abstract

In comparing the effectiveness of two treatments eligible patients arrive sequentially and must be treated at once. In this comparis we are treating patients not only derive information about the relative effectiveness of the treatments, but also to treat each patient in the best possible way that we can. Both goals might be compromised if a randomization scheme involving 50- allocation is used. The basic problem is how to assign patients different treatment groups to achieve a good compromise between the requirements of these two goal A new randomized adaptive treatmen assignment rule, the drop-the-lose rule, is proposed and analyzed.