ACA 2007

Doubly adaptive designs for "ethical" allocation of treatments in clinical trials

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joint with

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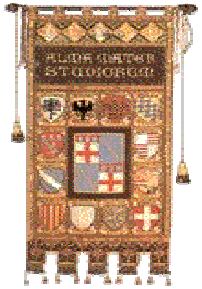


Clinical trials (patients as subjects)

MUST

- minimize potential harm to the patients presently under care

  The physician-patient relationship is based on the personal care principle (*Declaration of Helsinki,* 1964)

and

- maximize experimental information

Conflicting demands

individual-versus-collective ethics

A simple problem like comparing two treatments very difficult in clinical context

Randomized clinical trials as the gold standard

Is randomization part of the answer ?

- impartiality, eliminating selection bias...

- balancing prognostic factors...

or part of the problem ?

- randomized trials not always ethically and/or practically feasible

- Randomization v. inference

The view that ***randomized trials are the only scientifically valid ones*** *is mistaken*

(ROYALL, *Statistical Science* 1991)

Clinical Trials:

We look for

- early stopping
- a treatment allocation that moves away from simple randomization, in order to favour the better treatment(s)

Are "adaptive" trials the answer?

An **adaptive design** is a sequential rule that uses previously gathered information for choosing at each step (in a deterministic or randomized way) which treatment to allocate to the next patient(s) and/or whether to stop

Early research

Purpose of trial: Test treatment difference

Group Sequential methods in the1970s

Methods developed in manufacturing production transposed to clinical trials

- Allocation is 50-50 randomization
- **Stopping rules**

*Stop depends on data **i.e.** **response adaptive***

Interim monitoring of clinical trials

More recent research

- **adaptive allocations**

AND we wish to preserve some randomization

Allocation adapts to previous info:

- past allocations (**design adaptive**)
- past responses (**response adaptive, data dependent**)
- patients' covariates, including present patients'

Covariate adaptive = randomized, adapts to past allocations for balancing covariates

"Doubly" adaptive?

Doubly = adapts to past allocations + response

Trebly adaptive

C.A.R.A. = Covariate Adjusted, Response Adaptive, + to past allocations

Adaptive designs for ethical allocation of treatments in clinical trials

OUTLINE

✓Introduction

1. Design Criteria: Information and Ethics
2. Ideal allocations (TARGETS) for binary trials
3. Motives for being adaptive
4. Convergence properties of adaptive designs
5. Choice of target
6. Choice of design for information AND ethics
7. A proposal: Compromise criteria with adaptive weights

Notation

Comparison of 2 treatments T_1 , T_2

TRIAL

Sample size n

$$\pi = n_1 / n$$

proportion of allocations to treatment T_1

$\delta_k = 1$ $(\delta_k = 0)$ if k-th unit allocated to T_1 (T_2)

response $Y_k = \delta_k X_{1k} + (1-\delta_k) X_{2k}$

X_{1k}, X_{2k} the potential responses of k-th unit to T_1 , T_2

WITH COVARIATES

Z_k with or without interaction with treatments?

$$Z^{(n)} = (Z_1, Z_2, \ldots, Z_n)$$

BASIC MODEL

Distributional properties of X_{1k} (i.i.d) and X_{2k} (i.i.d),

Mean responses (μ_1, μ_2)

The probability of the patient's response depends only on the treatment and her/his covariates

$$\Pr(Y_{k+1} | \delta^{(k)}, Y^{(k)}, Z^{(k+1)}) = \Pr(Y_{k+1} | \delta_{k+1}, Z_{k+1})$$

Design criteria

Choice of experiment depends on

AIM of TRIAL

1. Testing $\mu_1 = \mu_2$
2. Estimating $\mu_1 - \mu_2$
3. Estimating μ_1 and μ_2 etc

and ethical, practical etc. considerations

+ RANDOMIZATION

Design criteria

Information

1. Power of test
2. Variance of estimated difference — **A-optimality**
3. Determinant of variance-covariance of estimators — **D-optimality**

Ethics

i. Total number of patients

ii. Expected number of patients allocated to “worse” treatment

iii. Expected number of “failures”

Each criterion (whether ethics or info) gives rise to an **ideal** allocation π^*

Ideal Allocations

for Binary Responses p_1 , p_2

INFERENCE

- Balance (D-opt) $n_1 = n_2$ $\pi_{Det}^* = ½$

- Neyman allocation (power ot test, variance of estimated difference):

$$\pi_{Tr}^* = \frac{\sqrt{p_1(1-p_1)}}{\sqrt{p_1(1-p_1)} + \sqrt{p_2(1-p_2)}}$$

depends on unknown parameters

ETHICS

- Both for ii. (allocated to worse treatment), and for iii. (failures)

$\pi^* = 0$ if $p_1 < p_2$ $\pi^* = 1$ if $p_1 > p_2$ any π if $p_1 = p_2$

Motives for being Adaptive

Just inference

- want **optimal** allocation but it depends on unknown parameters

Recursive ML

- want to converge to a target only partially known

Up-and-Down DURHAM, FLOURNOY (1994), BALDI, BORTOT & GIOV.,(2008)

Just ethics:

- at each step, want to favour treatment which performs better

Play-the-Winner ZELEN (1969)

- want to converge to ideal ethical allocation

Randomized Polya DURHAM, FLOURNOY & LI (1998)

Randomly reinforced urn design, MULIERE, PAGANONI & SECCHI *J.S.P.I.* (2006)

Motives for being Adaptive

Inference and randomization

- want balance and randomization — **Biased coins:** BCD, ABCD
- want D_A-opt and randomization — ACA (1982, 2002)

Ethics and randomization

- As P-the-W, but introduce randomness

Randomized P-the-W WEI and DURHAM (1978)

Drop-the-Loser IVANOVA (2003)

Generalized D-the-L SUN, CHEUNG and ZHANG *J.S.P.I.* (2007)

Inference and ethics

- want balance and desirable ("ethical") allocation

Doubly adaptive BCD (HU & ZHANG 2004), **DAWD** GERALDES ET AL, (2007)

This paper's approach

inference and ethics

Long-run ethics (convergence) as opposed to here-and-now

CONVERGENCE PROPERTIES OF ADAPTIVE DESIGNS

Treatment allocation sequence $\delta^{(n)} = (\delta_1, \ldots, \delta_n)$

Sequence of observed responses $Y^{(n)} = (Y_1, \ldots, Y_n)$

Sequence of covariates $Z^{(n)} = (Z_1, Z_2, \ldots, Z_n)$

Denote $\Im^{(k)} = (\delta^{(k)}, Y^{(k)}, Z^{(k+1)})$

Wlog always assume randomized)

- Start with $\Pr(\delta_1 | Z_1)$
- Stage *k*:

  $\Pr(\delta_{k+1} | \delta^{(k)}, Y^{(k)}, Z^{(k+1)})$ = probability of assigning treatment T_1 to next statistical unit, given observed data Y + past allocations δ + past and present covariates Z

If *n* large, there is scope for asymptotics

$\frac{N_1(k)}{k} = \pi_k$ proportion of allocations to T_1 after *k* steps is **random**

Design converges to a given target if $\pi_k \to \pi$ *almost surely.*

- observations **conditionally** independent
  (i.i.d. inference may no longer be valid)
- extra variability of the estimates (loss of power) due to the design

Convergence Theorems

(BALDI ANTOGNINI & G, *Seq Analysis* 2005)

If

$$\lim_{n\to\infty} \frac{1}{n} \sum_{1}^{n} \Pr(\delta_{k+1} = 1 \,|\, \Im^{(k)}) = \omega \qquad \textit{almost surely}, \quad \text{any } 0 < \omega < 1$$

then

- $N_1(n), N_2(n) \to \infty$ *a.s.*
- $N_1(n)/n, N_2(n)/n \to (\omega; 1-\omega)$ *a.s.*

Also, for binomial data (GLM), although observations no longer independent

- MLE's $(\hat{p}_1(n), \hat{p}_2(n))$ strongly consistent
- MLE's asymptotical normal
- asympt var-covar $\Sigma = \text{diag}\left(\frac{p_1 q_1}{\omega}; \frac{p_2 q_2}{1-\omega} \right)$

Applies to convergence of PW, RPW, Drop-the-Loser, Generalized D-the-L

$$\text{TARGET} = \frac{q_2}{q_1 + q_2}$$

Also

- Robbins-Simon-Starr (1967)
- Markovian designs (Erhenfest Urn, Polya Urn, ABCD….)
- Recursive SML designs

Recursive Maximum Likelihood

WU (1985, 1986) MELFI& PAGE (1999) ROSENBERGER & LACHIN (2002), BALDI ANTOGNINI & G. (2005)

Sequential ML DESIGN:

When target π^* is a function of p_1 and p_2, a "natural" solution is:

- start with n_0 observations on each treatment for initial parameter estimation
- at each step k (> $2n_0$)
  - estimate parameters sequentially by ML with all the data up to k
    - estimate target $\pi^*(p_1,p_2)$ by ML
      - allocate T_1 with probability equal to estimated target

If $0 < \pi*(p_1,p_2) < 1$ and $\pi*(p_1, p_2)$ continuous, then

- **SML design converges to $\pi*(p_1,p_2)$**
- **If target π^* is locally optimal, SML design is asymptotically optimal wrt unconditional inference**

More Convergence Theorems

1. (HU & ZHANG *Annals* 2004)

   SML design is asymptotically normal,

   expression for asymptotic variance

2. **C.A.R.A.** (ZHANG, HU, CHEUNG & CHAN *Annals* 2007)

   allocation rule $\pi(p_1, p_2, z)$

   - $\Pr(\delta_{k+1} | \delta^{(k)}, Y^{(k)}, Z^{(k+1)}) = \pi(p_1, p_2, Z_{k+1})$
   - estimate parameters and $\pi(p_1, p_2, z)$ by ML

   Under suitable conditions

   - **CARA design converges to π**
   - **MLE's strongly consistent, asymptotical normal**
   - **CARA design asymptotical normal**

Choice of targets

Choose one measure of efficiency Φ_I for information and one Φ_E for ethics

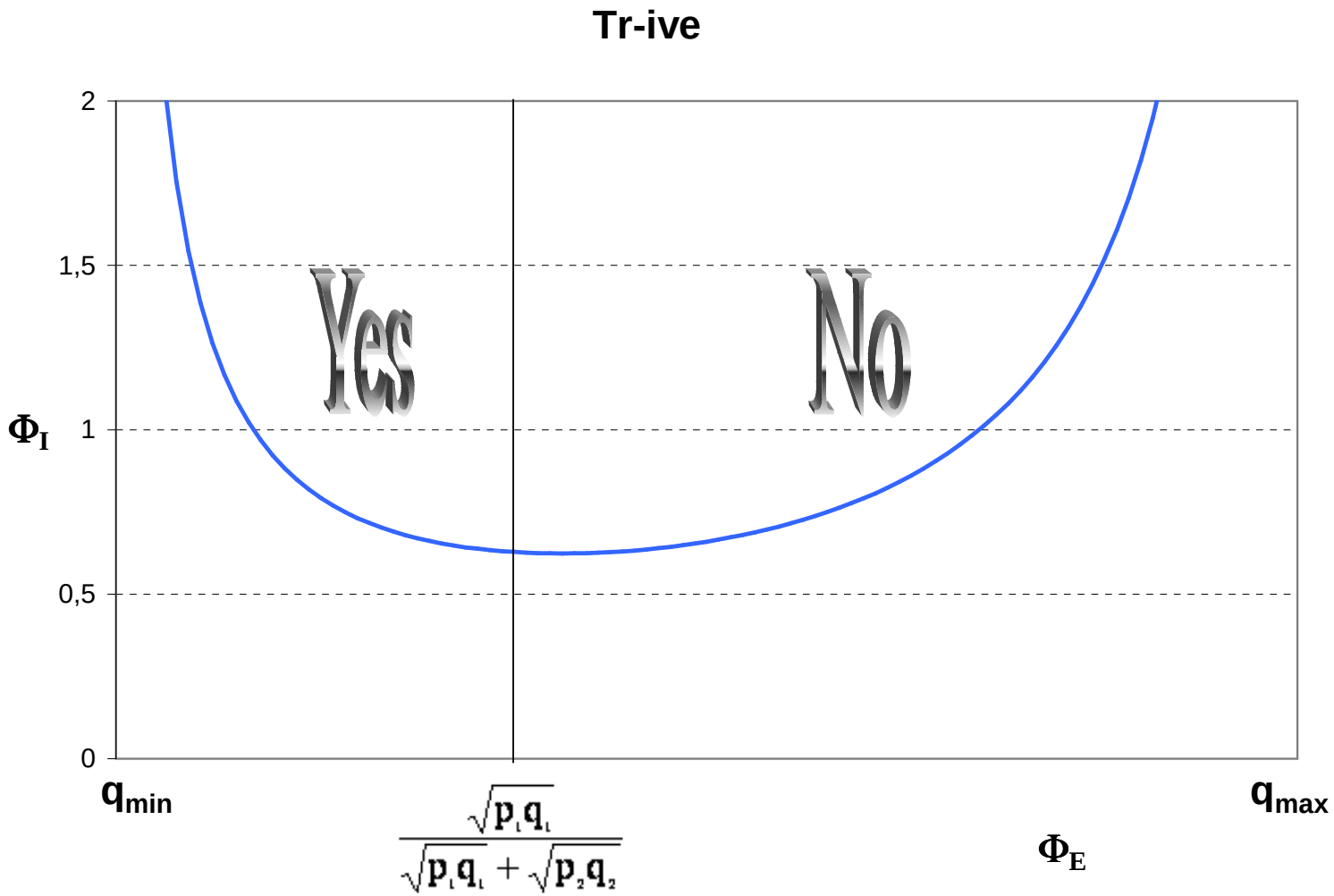
Each allocation π has two coordinates (Φ_E, Φ_I)

Target π_1 is **non-admissible** if it is **dominated** by target π_2

$$\Phi_E(\pi_1) \leq \Phi_E(\pi_2)$$
and
$$\Phi_I(\pi_1) \leq \Phi_I(\pi_2)$$

e.g. When info is trace

1. Play-the-Winner $\pi_{PW} = q_2/(q_1 + q_2)$ Target **not** always admissible
2. DAWD (GERALDES et al, 2007) Target **not** always admissible ($p_1 + p_2 > 1$)


Tr-ive
2
1,5
1
0,5
0
Yes
No
Φ_I
q_{min}
$\frac{\sqrt{p_1 q_1}}{\sqrt{p_1 q_1} + \sqrt{p_2 q_2}}$
q_{max}
Φ_E

Choice of Design for Info and Ethics

Two criteria: Φ_I measure of efficiency for information and Φ_E for ethics

1. Trade-off the experiments

Take two designs converging to respective optimal allocations. Take a "mixture" of designs

2. Target trade-off

Take a "mixture" of the optimal targets wrt two criteria. Find design converging to the mixture target

3. Trade-off the criteria

a) Optimise one criteria under a constraint for other

or

b) Find optimal allocation wrt a "mixture" of the criteria

Find design converging to this "optimal" target

Example of **2.**

DAWD (Doubly adaptive weighted difference)

GERALDES, MELFI, PAGE and ZHANG *J.S.P.I.* (2007)

$g(\cdot)$ governed by ethics $\qquad$ $h(\cdot)$ governed by balance

Compound Allocation: at each step assigns T_1 with probability

$$\lambda \cdot g\left(\hat{p}_1(n) - \hat{p}_2(n)\right) + (1-\lambda) \cdot h\left(2\frac{N_1(n)}{n} - 1\right)$$

Converges to the unique solution in [0,1] of the equation:

$$\pi = \lambda g\left(p_1 - p_2\right) + (1-\lambda) h\left(2\pi - 1\right)$$

λ = Weight to ethics $\qquad$ $1-\lambda$ = Weight to information

Example of **3. a)**

R-S-I-H-R ROSENBERGER et al., *Biometrics* (2001), TYMOFYEYEV, ROSENBERGER & HU *JASA* (2007)

- for given variance of estimated difference $p_1 - p_2$, π^* minimizes expected number of failures. Optimal target $\pi^* = \frac{\sqrt{p_1}}{\sqrt{p_1} + \sqrt{p_2}}$
- If implemented by SML, converges

A Proposal: Compromise criterion with Adaptive Weights

Combine (Φ_E, Φ_I) by means of a **compromise function:** ψ_λ

e.g.

$\psi =$ weighted arithmetic mean

$\psi =$ weighted geometric mean

$\psi =$ weighted harmonic mean

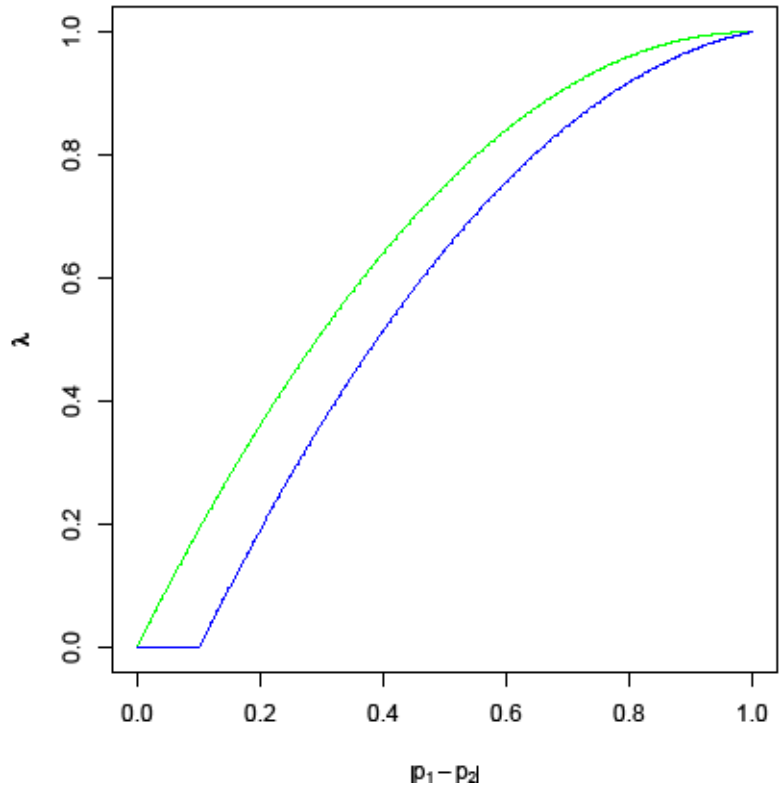
E.g. $\pi_{RSIHR} = \dfrac{\sqrt{p_1}}{\sqrt{p_1}+\sqrt{p_2}}$ corresponds to taking geometric mean of with equal weights

What "weight" to info and what to ethics?

Compromise Φ_E and Φ_I **by function** ψ_λ **with adaptive weights** λ , $1-\lambda$ that depend on p_1 , p_2

Ethical allocation more important if p_1 , p_2 *significantly different*

Weight to ethics λ increasing function of $|p_1 - p_2|$



if $|p_1 - p_2| \rightarrow 0$ ⇨ INFO and if $|p_1 - p_2| \rightarrow 1$ ⇨ ETHICS

- at each step the relative importance of Φ_E and Φ_I changes according to the observed data

$$\lambda_n = \lambda\left(|\,\hat{p}_1(n) - \hat{p}_2(n)\,|\right)$$

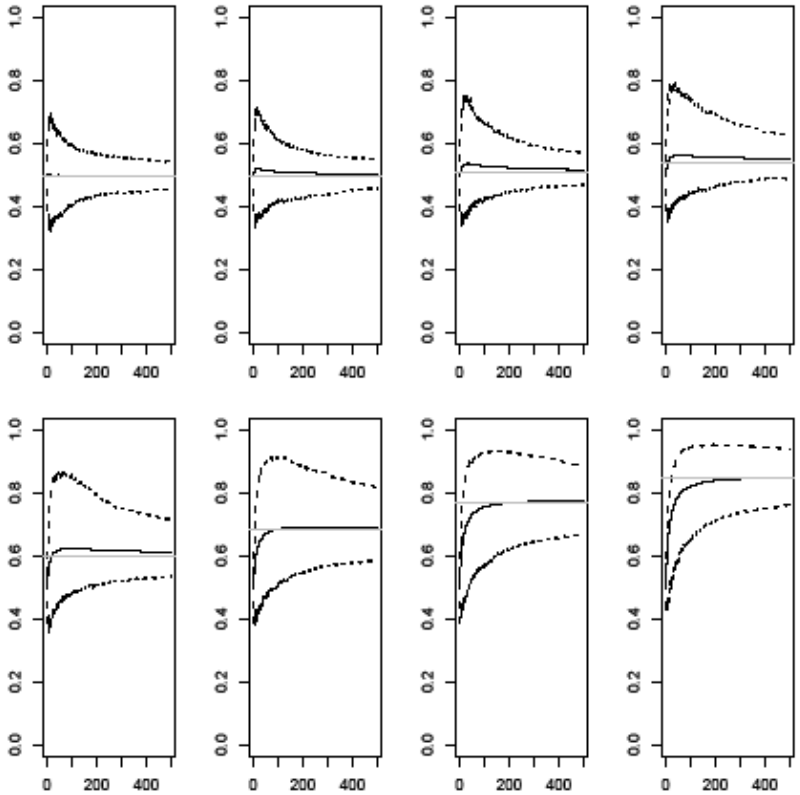
- at each step the target π_n optimises an adaptive combination of Φ_E and Φ_I

When implemented by SML

design **CONVERGES** to target which optimizes $\psi_\lambda(\pi)\ (0 < \pi < 1)$

Similar idea to BANDYOPADHYAY & BISWAS *B'ka* (2001)

SIMULATIONS



scenario	p_1-p_2	$\pi(p_1-p_2)$	*n*var
1	(0.5,0.5)	0.500	0.248
2	(0.6,0.5)	0.500	0.282
3	(0.7,0.5)	0.512	0.361
4	(0.8,0.5)	0.542	0.629
5	(0.9,0.5)	0.599	1.101
6	(0.9,0.4)	0.683	1.727
7	(0.9,0.3)	0.773	1.642
8	(0.9,0.2)	0.850	1.103

CONCLUSIONS

More research needed on

- **Asymptotic variance of design**

  speed of convergence needs improving

  (restrict randomization, Markovian)

- **Covariates** ROSENBERGER & SVERDLOV

  C.A.R.A optimality results?

- **Combined adaptive allocation and stopping rule**

  SOBEL and WEISS (1971), WEI and DURHAM (1978),

  BANDYOPADHYAY and BISWAS (1997, 2000, 2002, 2003), (BALDI ANTOGNINI & G. 2006)