A Regulatory Perspective on Adaptive Randomization*

H.M. James Hung
Division of Biometrics I, OB, CDER, FDA

Presented in 41st DIA Annual Meeting, Washington, DC, June 27, 2005

***The views presented are not necessarily of the U.S. Food and Drug Administration**

Acknowledgment

Thanks are due to Charles Anello for his comments and suggestions.

Outline

Fundamental of Clinical Trial

Fisher's 'Analyze as You Randomize'

Simple Randomization

Baseline Adaptive Randomization (BAR)

Guidance from Literature on BAR

Some Regulatory Concerns

Summary

Fundamental of Clinical Trial

Randomization (random allocation)

to achieve balance in all known and unknown, observed and unobserved covariates (e.g., prognostic factors) at baseline

Baseline balance is "expected" to be achieved in the long run (in average). Apparent or accidental imbalance may occur in any individual trial.

Blinding

to minimize operational bias and selection bias

Fisher's 'Analyze as You Randomize'

Base statistical inference on design (use design to generate p-value of statistical test).

The frame of statistical inference is based on the probabilistic treatment assignment in all possible ways that the design can generate, conditional on the observed outcome and covariates of the patients in the trial.

This usually cannot be approximated by simulating trial outcome according to some population model.

Simple Randomization

Method 1: Sample sizes in each treatment group are known exactly a priori

each group size is fixed exactly at m

Method 2: Target sample size is established but final sample size is not known with certainty (most common in large clinical trials)

target sample size is fixed at $2m$ but the final sample sizes are (n_1, n_2) where n_1 and n_2 often differ from m and $n_1+n_2 \approx 2m$

Simple Randomization (Cont'd)

Under this design, ANOVA approximates randomization test properly.

For large trials, simple randomization is satisfactory in balancing [Lachin (1988)] on baseline covariates.

Simple Randomization (Cont'd)

For small or moderate trials, baseline imbalance may appear (more often) and is certainly of concern in practice, even when it is due to chance alone.

Adjusting for covariates that appear to be unbalanced from post hoc examination of data is not good statistical practice.

- prespecify adjustment for all known prognostic covariates in statistical analysis plan

Simple Randomization (Cont'd)

To improve balancing, stratification can be used with simple randomization (e.g., patients can be stratified by age and/or gender) and simple randomization is carried out within each stratum.

- restriction in # of covariates to stratify on

Random permuted blocking with a small block size can also be used to improve balancing at the local level, e.g., block size of four: (ABBA), (ABAB), (BAAB), …

- high predictability if cell totals are known

Baseline Adaptive Randomization (BAR)

Treatment assignment of the next patient, or the probability of the assignment, determined to minimize a measure (need pre-specify?) of overall covariate imbalance when that patient's covariate values are considered

- probabilistic (e.g., Pocock-Simon)
- deterministic (e.g. Taves minimization)

Baseline Adaptive Randomization

Ex. To improve balance on gender distribution, probabilistic BAR (p = prob. of assigning A)

Pt →	M	M	F	M	F
p	0.5	0.3	0.5	0.4	0.8
trt	A	B	B	A	A

deterministic BAR

Pt →	M	M	F	M	F
p	0.5	0.0	0.5	0.0	0.5
trt	A	B	B	B	A

Baseline Adaptive Randomization

Probabilistic procedure

- do better balancing than simple randomization
- random treatment allocation
- design-based inference is available
  e.g., probability distribution of test generated by re-randomizing patients conditional on the order of enrollment of the patients
- statistical analysis can be based on a population model that the patients in the trial come from a homogeneous population (unverifiable assumption)

Baseline Adaptive Randomization

Deterministic procedure

- do better balancing than probabilistic BAR
- largely non-random treatment allocation (except for 1st few patients or for ties)
- permutation test might not be available unless patient entry into the trial is a random process (unverifiable assumption)
- statistical analysis is mostly based on a population model that patients in the trial are from a homogeneous population (unverifiable assumption)

Guidance from Literature on BAR

Balancing on covariates tends to decrease variance of estimates.

Unadjusted standard test has conservative type I error with BAR.
Adjusted test (adjusting for covariates for balancing) has appropriate significance level.

Randomization methods do not allow tests of alternatives or generation of confidence intervals (model-based methods still needed)

Guidance from Literature on BAR

BAR can be difficult if interactions between factors for balancing can be predicted.

Prefer to incorporate a random vector to further reduce predictability and to allow calculation of a randomization test (if needed).

If there are time trends in the patient baseline characteristics or strong correlation between outcome and patient entry order, then the standard tests w/o proper adjustment are conservative (**??**).

Guidance from Literature on BAR

Balance on unknown covariates with BAR cannot be worse than with simple randomization.

Balancing with BAR can improve efficiency of treatment effect estimate.

For deterministic BAR, predictability is high with knowledge of marginal totals and algorithm

Some Regulatory Concerns (1)

With BAR, analysis must be adjusted for the covariates employed for balancing in order to yield tests of proper size.

However, unlike quantitative response variable, other types of response variables (e.g., binary, time to event, categorical) often rely on a nonlinear model for covariate adjustment (e.g., logistic, PH regression).

Some Regulatory Concerns (1, Cont'd)

Even under simple randomization, the covariate adjustment using nonlinear model can result in a smaller p-value but a larger variance of the effect estimate than unadjusted analysis in an individual trial. That is, the treatment effect estimate is larger than that produced by unadjusted analysis.

Will BAR have additional adverse impact on p-value or type I error rate of standard test?

- In practice, need to compare the results of covariate adjusted analysis with the results of re-randomization test

Some Regulatory Concerns (2)

In the presence of a strong time trend in patient's baseline characteristics, the literature suggests that standard tests tend to have the type I errors distorted toward conservative side under BAR ← all based on simulation studies

Will the distortion never be anti-conservative? This question is related to Question 1).

- In practice, need to compare the results of covariate adjusted analysis with the results of re-randomization test

Some Regulatory Concerns (3)

Under BAR, are there any additional difficulties in handling dropouts in analysis? probably yes, because analyses need adjustment for covariates for balancing in the model.

- not even sure of how to handle missing values due to MCAR

Some Regulatory Concerns (4)

In many situations, interim analysis and data monitoring are necessary. So is some design modification (e.g., sample size re-estimation).

If BAR is used, **what will the potential impact be on interpretation of trial results?**

- statistical validity

  Are the common group-sequential methods still applicable?

- logistics and trial conduct issues

Some Regulatory Concerns (5)

With deterministic BAR, designed-based inference might not be possible (sample space might be too small?)

- conditional on patients' entry order?
- conditional on covariates considered?
- conditional on patients (assuming patient entry is random)?

High predictability

- how to verify that this is not an issue for a practical application

Summary

Probabilistic BAR may help balancing on baseline covariates in small trials.

- need to prespecify allocation probability rule
  select allocation probability $\Rightarrow$ low predictability
- need to check validity of standard asymptotic test
  compare with re-randomization test
- be aware of potential compromise on blinding
  need SOP and document trial management
- need a pre-specified plan to deal with unexpected strong time trends in covariates in analysis

Summary

Logistics needs to be carefully considered in use of adaptive randomization.

- need to anticipate and deal with logistical problems at the design stage
- SOP may be needed
- have 3rd independent party execute allocation?
- how to avoid operational errors due to practical complexity

Summary

Deterministic BAR is discouraged because of uncertainty about analysis and interpretation, though some argue that it is mostly harmless.

- no ability to do design-based inference unless patient entry is random (unverifiable assumption)

Why taking risk of possible compromise on false positive rate to seek a complete balance?

- treatment allocation may be predictable.

Why taking risk of selection or operational bias?

Selected References

Busye and McEntegart (2004, Applied Clinical Trials)

CPMP Points to Consider document on Adjustment for Baseline Covariates (2003)

Forsythe (1987, Computational Statistics & Data Analysis)

Frane (1998, Drug Information Journal)

Halperin and Brown (1986, Statistics in Medicine)

ICH E-9 guidance on statistical principles for clinical trials

Kalish and Begg (1987, Controlled Clinical Trials)

Lachin (1988, Controlled Clinical Trials)

Lachin, Matts, Wei (1988, Controlled Clinical Trials)

Ohasi (1990, Environmental Health Perspectives)

Permutt and Grosser (2004, SOCT talk)

Pocock and Simon (1975, Biometrics)

Scott, McPherson, Ramsay, Campbell (2002, Controlled Clinical Trials)

Selected References

Taves (1974, Clinical Pharm. Ther.)
Weir and Lees (2003, Statistics in Medicine)
Green (2004, presentation in DIA-Japan workshop)
Hagino, Hamada,Yoshimura, Ohashi (2004, presentation in DIA-Japan workshop)
Ohashi (2004, presentation in DIA-Japan workshop)
Rosenberger and Lachin (2002, book)