Randomization Challenges and Solutions in Adaptive Design Trials

Olga M. Kuznetsova
Merck, Sharp & Dohme, Corp.

Acknowledgments

- Great thanks to Yevgen Tymofyeyev, in collaboration with whom novel techniques for unequal allocation described in this presentation were developed

Contents

- Special needs of adaptive design studies require advanced randomization techniques
- Expanding advanced randomization techniques to unequal allocation while preserving the allocation ratio at every step
  - Techniques that promote balance in baseline covariates
  - Techniques that facilitate efficient drug use in multi-center studies
  - Techniques that keep the allocation ratio close to the intended ratio in small cohorts
- Regulatory considerations
- Conclusions

Conflicting Needs of Accelerated Development

- AD studies are early in drug development
  - Limited drug supplies
- Fast enrollment requires large number of centers
  - Large volume of drug is needed to stock centers
  - Fast drug re-supplies required
- Require randomization techniques that facilitate economical drug use in multi-center trials

Interim Decisions Made on a Small Sample

- Treatment arms need to be similar in distribution of important baseline covariates
  - Imbalance could lead to biased results
  - In a small sample, randomization that ignores covariates does not guarantee groups similarity
  - Requires a randomization procedure that enforces balance in covariates
  - Often means dynamic allocation

Unequal Allocation is Common in Adaptive Design Trials

- Dose-finding studies
  - Large number of treatment arms
  - Allocation ratio for the next cohort depends of doses performance in earlier cohorts
- Two-stage designs
  - Stage II allocation ratios differ for old arms vs. new arms
- Studies with sample size re-estimation and >2 arms
- Large block size is a common problem

Operational Challenges

- Uncertainty in the allocation ratio for the next cohort
  - Determined after interim analysis
  - Prepare for several possible scenarios
  - Ship drug supplies to the sites in advance to support all options
- Blinding issues brought on by
  - Changes in the allocation ratio
  - Drug supplies scheme

Advanced Randomization Techniques In Studies With Equal Allocation (see Refs)

- Advanced randomization techniques were developed to deal with many of these challenges in studies with equal allocation
  - Techniques that promote balance in baseline covariates
    - Minimization (covariate-adaptive procedures); hierarchical dynamic balancing
  - Techniques that facilitate efficient drug use in multi-center studies
    - Modified Zelen's approach; dynamic allocation with partial block supplies sent to centers
  - Techniques that keep the allocation ratio close to the intended ratio in small cohorts
    - Maximal procedure; biased coin design; big stick design

Expanding an Advanced Randomization Technique to Unequal Allocation is Often Tricky

- Direct expansion often results in variations in the allocation ratio from allocation to allocation
- Need to expand a technique in a way that preserves the allocation ratio at every allocation [K&T 2011, 2012]

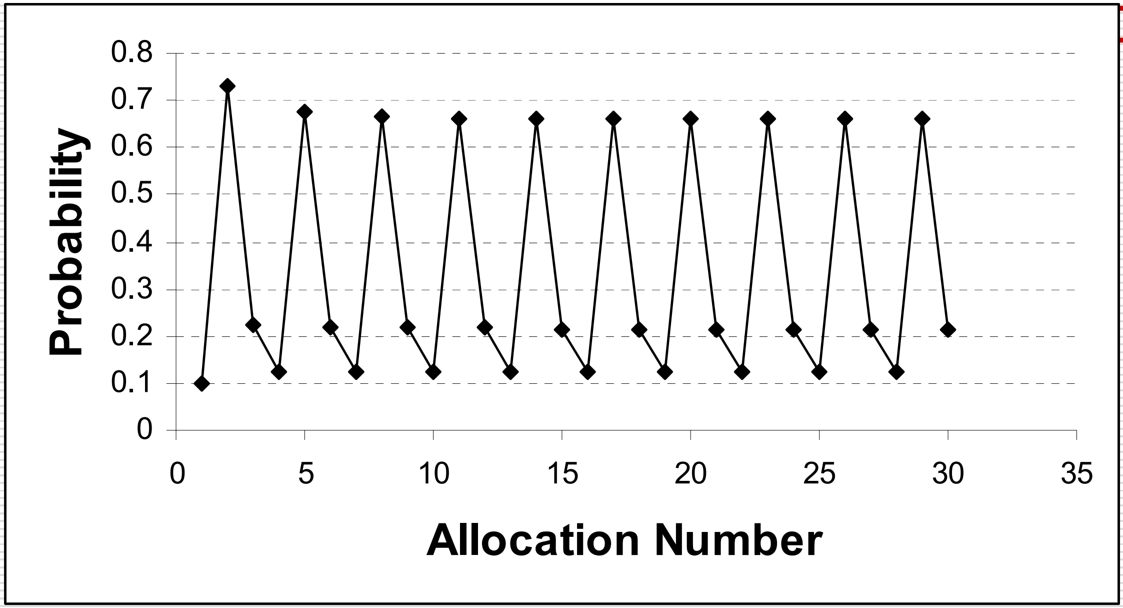
Example 1. Minimization

- Covariate-adaptive procedure developed for equal allocation [Taves 1974, Pocock and Simon 1975]
- Treatment assignments (T=1,…, K) determined dynamically
- New patient's covariates are recorded
- Imbalance metric is calculated for each treatment; as if the new patients is assigned T=1, .., k
  - across all randomized patients and the new patient
- The treatment that leads to least imbalance is "the preferred treatment"
- Preferred treatment assigned not with certainty, but with high probability (ex.: p=0.9);
  - other treatments assigned with probability (1-p)/(1-k)

Problem with Direct Expansion of Minimization to Unequal Allocation

- The concept of the “preferred treatment” does not work well for unequal allocation
- For 1:1 allocation to Active: Control that balances only on treatment totals, imbalance metric is |Na-Nc|
- For 2:1 allocation, imbalance metric is |Na-2Nc|
- Preferred treatment minimizes |Na-2Nc| after the allocation
- When the preferred treatment is assigned with certainty, an allocation sequence is: ACA ACA ACA…
- When random element is added, probability of Control assignment is still lower than 1/3 at 1, 3, 4, 6th … allocations and higher than 1/3 at 2, 5, 7^{th}, … allocations

Probability to Allocate Control with 2:1 Biased Coin Minimization that Balances Only on Treatment Group Totals by Allocation Number



- ←2:1 Biased Coin Minimization by Han, Enas, and McEntegart 2009
  - If Active is preferred, it is assigned with p=0.9
  - If Control is preferred, it is assigned with p=0.8

- Probability to allocate Control is not 1/3, but varies with Allocation Number
- When minimization balances on covariates, variations in probability of Control assignment depend on sequence of covariates; less pronounced

Variations in Allocation Ratio from Allocation to Allocation Can Cause Bias

- Variations provide potential for selection and evaluation bias even in double-blind studies [Kuznetsova & Tymofyeyev StM 2011, 2012]
  - Investigator might allocate sicker patients when he knows the probability to allocate Placebo is lower (2nd, 5th, 8th, in a center)
  - Active group will have sicker patients
- Provide potential for accidental bias
- Lead to problems with randomization test
  - Proschan et al. [2011], K&T [2012]

Solution: Allocation Ratio Preserving Expansions to Unequal Allocation

- K arms $G_1, \ldots, G_k$
- Q_1:Q_2: … : Q_k allocation ratio
- $S = Q_1 + Q_2 + \ldots + Q_k$ *is* the "block size"
- First, execute equal allocation to S “fake” treatments ($F_1, \ldots, F_S$)
- Map F_1 - F_{Q1} to G_1; map F_{Q1+1} – F_{Q1+Q2} to G_2;…; map F_{S-Qk} – F_S to G_S.
- Then, Q_1:Q_2: … : Q_k allocation ratio will be preserved at every allocation
  - Details in [K&T 2012]

Other Randomization Techniques That Promote Balance in Baseline Covariates

- Dynamic hierarchical allocation procedures [Signorini 1993, Heritier 2005] achieve balance in a number of covariates order in importance
- Can be expanded to unequal allocation in the same way as minimization [K&T JSM2011]

Example 2. Modified Zelen's Approach in a Multi-Center Study

- 4-arms: Low Dose, High Dose, Placebo, Control
  - Equal allocation
  - Stage I of a Two-Stage Design
- Interim analysis of 80 patients (20 per arm)
- 40 centers with 2 patients on average (range 1-7)
- Only 1 block of supplies per center (4 kits) available at study initiation
  - Not enough to support central randomization
- Stratified by center randomization might lead to poor balance in TRT assignments at interim analysis
  - Most of the blocks are only half-filled

Solution: Dynamic Allocation with Modified Zelen's Approach (MZA)

- Proposed by Zelen [1974] for 1:1 allocation
- Modified and expanded to equal allocation to >2 arms by McEntegart [2003] and colleagues [Morrissey, McEntegart, Lang 2010]
- Provided by IVRS vendors

MZA: Patient is Allocated to the First Unused Treatment on the Allocation Sequence Available at His Center

- Permuted block allocation sequence generated AN:

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16

- 4 centers C1-C4
- 4 Kits per center (1 block)
- N –order of arrival
  AN – order in sequence

C1		C2		C3		C4	
N	AN	N	AN	N	AN	N	AN
2	2	1	1	3	3	5	5
11	10	7	6	4	4	8	8
		12	14	6	7	10	11
				9	9	13	12
						14	15

- The 6th Patient should get Orange
- No Orange at C3
- The 6th Patient receives Blue
- Orange backfilled by the 7th patient

How Modified Zelen's Approach Works

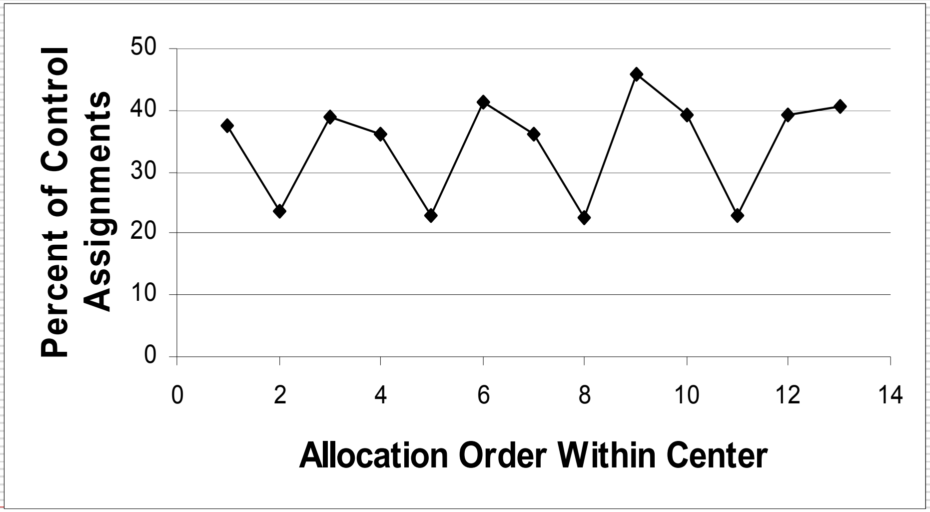
- Recap:
  - A block of 4 treatment kits is made available at each center at study start
  - Permuted block allocation sequence with Block Size 4 is generated
  - Patient is allocated to the first treatment in the allocation sequence available at his center
  - When the 1st block is used by the center, 2nd block becomes available...
  - Gaps in the allocation sequence are backfilled
  - Permutation at each site is determined dynamically
- Excellent balance in treatment assignments as most blocks on the schedule are filled [MML 2010]

Other Uses of Modified Zelen's Approach

- Can be stratified by several factors
  - Great stratification option when there is not enough drug for central randomization
- Can be used in conjunction with minimization or hierarchical dynamic balancing

Expanding Modified Zelen's Approach to Unequal Allocation

- Cannot just substitute equal allocation blocks with unequal allocation blocks in the algorithm
- This will make allocation ratio vary with order of enrollment within a center
- Simulations of "naïve" MZA expansion in an 80-center study with 1:2 allocation to Control and Active



Example 3. Dynamic Allocation with Partial Block Supplies Sent to Centers [MML 2010]

- Excellent technique when the block size is much larger than center size
  - Sending a whole block of kits to each site will lead to drug waste
- Example: 10-arm multi-center study with equal allocation and center size ~4

Solution: Dynamic Allocation with Partial Block Supplies Sent to the Centers [MML 2010]

- Similar to MZA, allocation schedule with block size 10 is generated
- Each site receives not a whole block of 10 kits, but a partial block of 4 kits
- To that end, separate random sequence is generated for drug supplies
  - Sequence is cut in 4-kit segments
  - Segments are distributed across centers
  - Different centers get different sets of 4 kits
- Patient is allocated to the first unused treatment on the allocation schedule available at his site

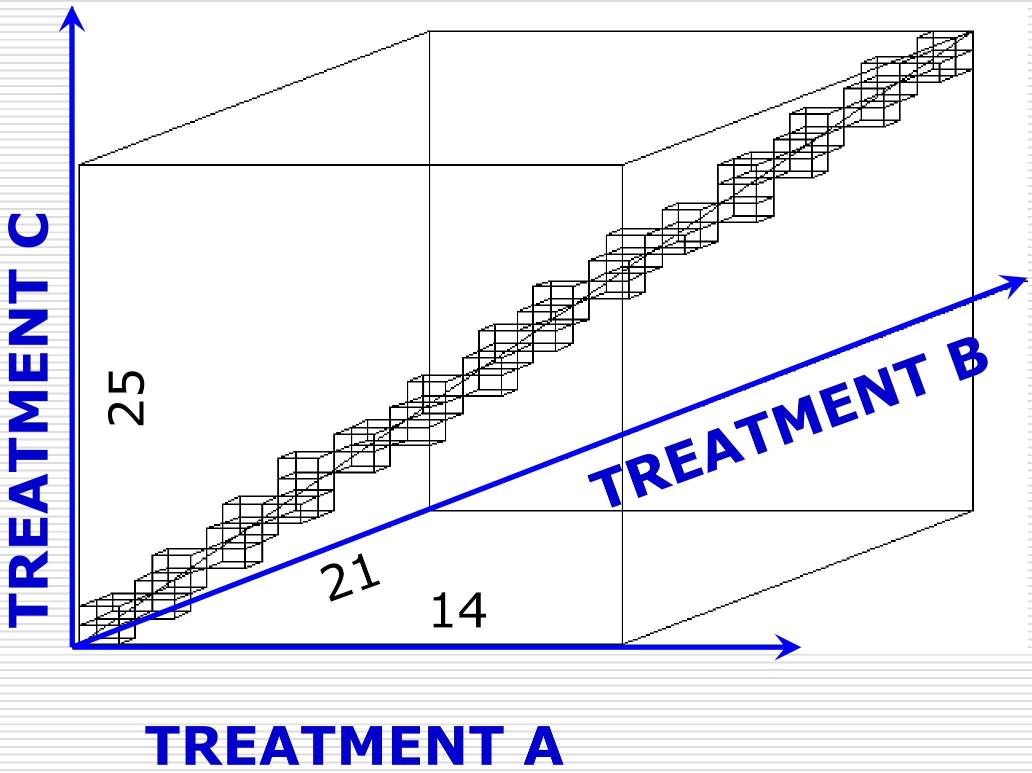
Expanding Dynamic Allocation with Partial Block Supplies Sent to a Center to Unequal Allocation

- Extremely useful when dealing with a large block size in multicenter studies
- Execute the allocation using *S* Fake Treatments
- Important extra step: ensure symmetry with respect to *S* Fake Treatments when defining the partial blocks to be sent to the sites
  - How to do it is described in [K&T CCT2011]

Example 4. Inconvenient Allocation Ratio

- Adaptive dose ranging study
  - Cohort size: 10-15 patients
- The allocation ratio for the next cohort of patients is 14:21:25
- Permuted block size = 60
  - Too large for a cohort of 10-15
- Could lead to an allocation ratio very different from the targeted ratio
- Solution – Brick Tunnel Randomization [K&T StM2011]

Brick Tunnel Randomization for 14:21:25 Allocation to Treatments A, B, and C



- Instead of occupying the whole 14×21×25 permuted block, allocation sequences are constrained to a chain of unitary cubes pierced by the diagonal

Utility of Brick Tunnel Randomization

- Preserves the allocation ratio at every step
- Provides good approximation of the targeted allocation ratio even for short cohorts of 10-15 subjects
- Allows to allocate any number of patients not fixed in advance
- Can be used in studies with response-adaptive allocation
  - approximates targeted allocation better than when each patient is allocated independently.
- Can be expanded to cover a wider strip around the allocation ray (useful in 2-group open-label studies)
- Alternative: constrained randomization

Regulatory Considerations

- Draft Guidance on Adaptive Designs discusses response-adaptive randomization where allocation ratio depends on observed responses
- Guidance has no mention of utility of dynamic allocation in adaptive design studies
- Obtaining concurrence of regulatory agencies whenever dynamic allocation is planned in a study is advisable
  - Most critical for pivotal studies
- Having general regulatory input into use of dynamic allocation techniques, in particular those that facilitate efficient drug use in multi-center studies, would help drug development

Conclusions

- In adaptive design trials, advanced randomization techniques help dealing with conflicting needs of accelerated development
  - provide balance in baseline covariates in a small interim analysis sample
  - efficiently manage limited or expensive drug supplies in multi-center studies
  - deal with an inconvenient allocation ratio common to many adaptive designs
- These techniques are very useful in studies with unequal allocation
- When expanding allocation techniques to unequal allocation, preserve the allocation ratio at every allocation

References

- Byrom B, McEntegart D. Adaptive infrastructure. In: Adaptive Designs in Pharmaceutical/Clinical Development. Editor Shein-Chung Chow. Chapman & Hall/CRC, Taylor and Francis. October 2010
- Efron, B. (1971). Forcing a sequential experiment to be balanced. Biometrika 58 403-417.
- Food and Drug Administration. Draft Guidance for Industry: Adaptive Design Clinical Trials for Drugs and Biologics. Available at www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM201790.pdf. Released on February 25, 2010, for public comments
- Frane JW. A method of biased coin randomization, its implementation, and its validation. Drug Information Journal, Vol. 32, pp.423-432, 1998. DOI:0092-8615/98
- Gaydos B, Krams M, Perevozskaya I, Brets F, Liu Q, Gallo P, et al. PhRMA Working Group on Adaptive Designs: adaptive dose-response studies. *Drug Information Journal* 2006; **40**: 451-461 .
- Han B, Enas NH, McEntegart D. Randomization by minimization for unbalanced treatment allocation. *Statistics in Medicine* 2009; 28: 3329-3346. DOI:10.1002/sim.3710
- He W, Kuznetsova OM, Harmer MA, Leahy CJ, Anderson KM, Dossin DN, Li L, Bolognese JA, Tymofyeyev Y, Schindler JS. Practical considerations and strategies for executing adaptive clinical trials. Drug Information Journal 2012 46: 160-174. DOI: 10.1177/0092861512436580

References

- Heritier S., Gebski V., Pillai A., Dynamic balancing randomization in controlled clinical trials. *Statist.Med*.2005; 24:3729-3741. DOI:10.1002/sim.2421
- Kuznetsova O, Ivanova A. Allocation in Randomized Clinical Trials. In Dmitrienko, A., Chuang-Stein, C., D'Agostino, R. eds. *Pharmaceutical Statistics Using SAS*. SAS Press: Cary, NC, 2006
- Kuznetsova OM, Tymofyeyev Y. Brick Tunnel Randomization For Unequal Allocation to Two or More Treatment Groups. Statist. Med 2011, 30: 812—824. DOI: 10.1002/sim.4167
- Kuznetsova OM, Tymofyeyev Y. Preserving the Allocation Ratio at Every Allocation with Biased Coin Randomization and Minimization in Studies with Unequal Allocation . Statist. Med 2012 31: 701-732; DOI: 10.1002/sim.4447.
- Kuznetsova OM, Tymofyeyev Y. Expansion of the modified Zelen's approach randomization and dynamic randomization with partial block supplies at the centers to unequal allocation. Contemporary Clinical Trials 2011; 32: 962–972; doi:10.1016/j.cct.2011.08.006.
- Kuznetsova OM, Tymofyeyev Y. Expansion of the Modified Zelen's Approach Randomization and Dynamic Randomization with Partial Block Supplies at the Centers to Unequal Allocation. JSM Proceedings; Miami Beach 2011.
- Kuznetsova OM. Randomization Schedule. In: D'Agostino R, Sullivan L, Massaro J, editors.Wiley Encyclopedia of Clinical Trials. Hoboken: John Wiley &Sons., Inc; 2008. DOI: 10.1002/9780471462422.eoct314.

References

- McEntegart D. Blocked Randomization. In: D'Agostino R, Sullivan L, Massaro J, editors.Wiley Encyclopedia of Clinical Trials. Hoboken: John Wiley &Sons., Inc; June 13 2008. DOI:10.1002/9780471462422.eoct301.
- McEntegart D. The pursuit of balance using stratified and dynamic randomization techniques: an overview. Drug Information Journal 2003; 37:293–308.
- McEntegart, D. Forced Randomization When Using Interactive Voice Response Systems. Applied Clinical Trials 2002 August; 2-10.
- Morrissey M, McEntegart D, Lang M. Randomisation in double-blind multicentre trials with many treatments. *Contemporary Clinical Trials* 2010; **31**: 381-391. DOI: 10.1016./j/cct/2010.05.002
- Nishi T, Takaishi A. An extended minimization method to assure similar means of continuous prognostic variable between treatment groups. Japanese Journal of Biometrics 2003; 24: 43-55.
- Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics 1975; 31:103–115.

References

- Proschan M., Brittain E., and Kammerman L. Minimize the use of minimization with unequal allocation. Biometrics 2011 DOI: 10.1111/j.1541-0420.2010.01545.x.
- Rosenberger, WF, Lachin, JM. *Randomization in Clinical Trials*. John Wiley & Sons, New York, 2002.
- Rosenberger, WF, Sverdlov, O. (2008) Handling covariates in the design of clinical trials. Statistical Science, 23: 404-19.
- Scott, NW, McPherson GC, Ramsay, CR, Campbell, MK: The method of minimization for allocation to clinical trials: a review. Controlled Clin Trials 23:662-674, 2002.
- Signorini DF, Leung O, Simes RJ, Beller E, Gebski VJ. Dynamic balanced randomisation for clinical trials. *Statistics in Medicine* 1993;12:2343–2350.
- Song, C., Kuznetsova, O.M. (2003) Implementing Constrained or Balanced Across the Centers Randomization with SAS v8 Procedure PLAN, PharmaSUG 2003 proceedings, pp 473-479.

References

- Taves D. Minimization: a new method of assigning subjects to treatment and control groups. Clinical Pharmacology and Therapeutics 1974; 15:443–453
- Therneau TM: How many stratification factors are "too many" to use in a randomization plan? Control Clin Trials 14(2):98-108, 1993.
- Youden WJ. Inadmissible random assignments. *Technometrics* 1964; **6**: 103-104.
- Youden WJ. Randomization and experimentation. *Technometrics* 1972 14: 13-22.
- Zelen, M. The randomization and stratification of patients to clinical trials. *Journal of Chronic Disease* 1974; **27**: 365-375.
- Zhang L., Rosenberger W. Optimal Response-Adaptive Randomization for Clinical Trials. In: Adaptive Designs in Pharmaceutical/Clinical Development. Editor Shein-Chung Chow. Chapman & Hall/CRC, Taylor and Francis. October 2010