Allocation Ratio Preserving Randomization Procedures

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Based on joint works with Yevgen Tymofyeyev and Victoria Plamadeala Johnson

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- Why do we need to preserve the unconditional allocation ratio
- ARP unequal allocation expansion of any equal allocation procedure through mapping
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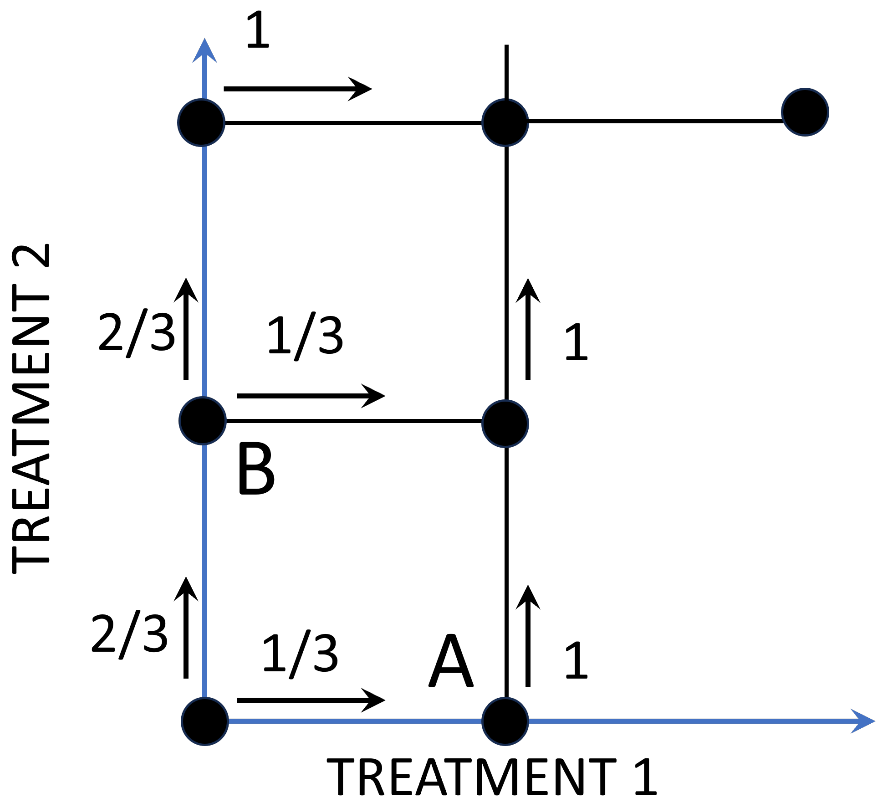
History

- The problem was first identified by Proschan M, Brittain E, and Kammerman L.
    - “Minimize the use of minimization with unequal allocation”. *Biometrics* 2011
- They noted that in a study with a 2:1 allocation following some version of minimization the distribution of the re-randomization test statistics was not centered around 0 but shifted, lowering the power of the re-randomization test
    - They attributed this issue to some unknown properties of minimization
- Kuznetsova & Tymofyeyev [2012] showed that the issue is caused by the variations in the unconditional allocation ratio in the version of unequal allocation minimization used in the study where this phenomenon was observed
    - Introduced term Allocation Ratio Preserving (ARP) procedure: unconditional AR is constant
    - Derived the value of the shift based on a sequence of unconditional probabilities of allocation
- It happens to all non-ARP unequal allocation procedures, fixed or dynamic
- The need for ARP property is often overlooked with novel unequal allocation procedures
- Non-trivial to satisfy when expanding allocation procedures to unequal allocation

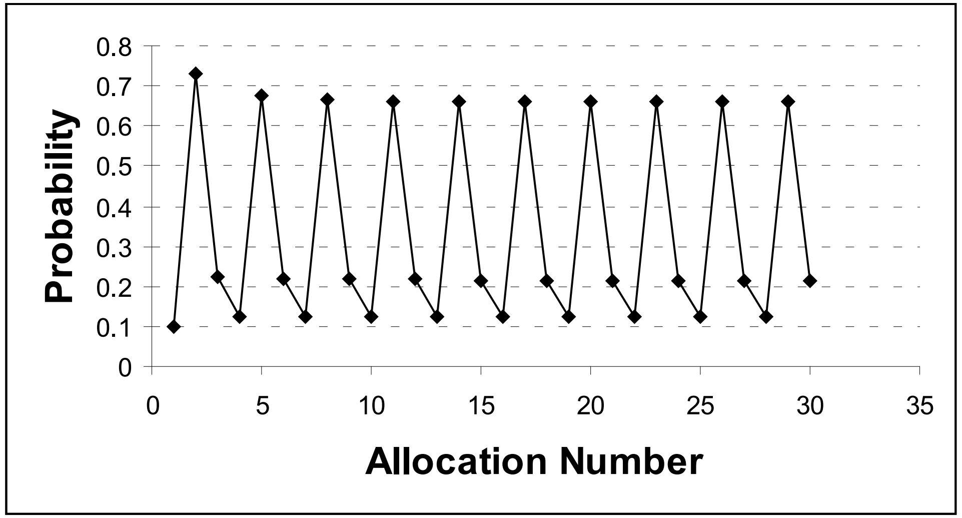
Example 1: Naïve Expansion of the Big Stick Design to 1:2 Allocation Does not Preserve the Unconditional Allocation Ratio



- 2-arm 1:1 Big Stick Design with MTI=1: a subject is randomized in 1:1 ratio whenever $|N_2 - N_1| \leq 1$; otherwise, allocated to the allowed treatment
- Naïve 1:2 expansion: subject is allocated in 1:2 ratio whenever the normalized imbalance $|N_2/2 - N_1| \leq 1$
- Let us depict allocation to Treatment 1 by a step to the right; allocation to Treatment 2 by a step up on a unitary grid
- Probability to end in node A after the 1st allocation is 1/3; in node B – 2/3
  - From A, only allocation to Treatment 2 is allowed
- Thus, the unconditional probability of Treatment 1 allocation to the 2nd subject is 2/3*1/3=2/9 instead of 1/3
- The ARP property is violated
- The same is the case for $|N_2/2 - N_1| \leq b$

Example 2. Expansions of Biased Coin Randomization

- For equal allocation, underrepresented arm is the preferred arm; it is allocated with probability p>0.5.
- For 1:2 allocation, the preferred arm is the arm that, if allocated, minimizes the normalized imbalance $|N_2/2-N_1|$.
  - Naïve expansion: preferred arm is allocated with probability p^H, non-preferred with probability p^L (for example, 0.8 and 0.2)
  - Han et al. 2009 expansion: probability p^H depends on which arm is the preferred arm:
    p^H =0.8 for arm 1,
    p^H =0.9 for arm 2.



- Figure on the right shows unconditional allocation probabilities of Treatment 1 with 1:2 Han et al. [2009] expansion
- Note low-high-low-low-high-low-low pattern
- Common problem for expansions based on normalized imbalance

From: 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: 701-723; DOI: 10.1002/sim.4447.

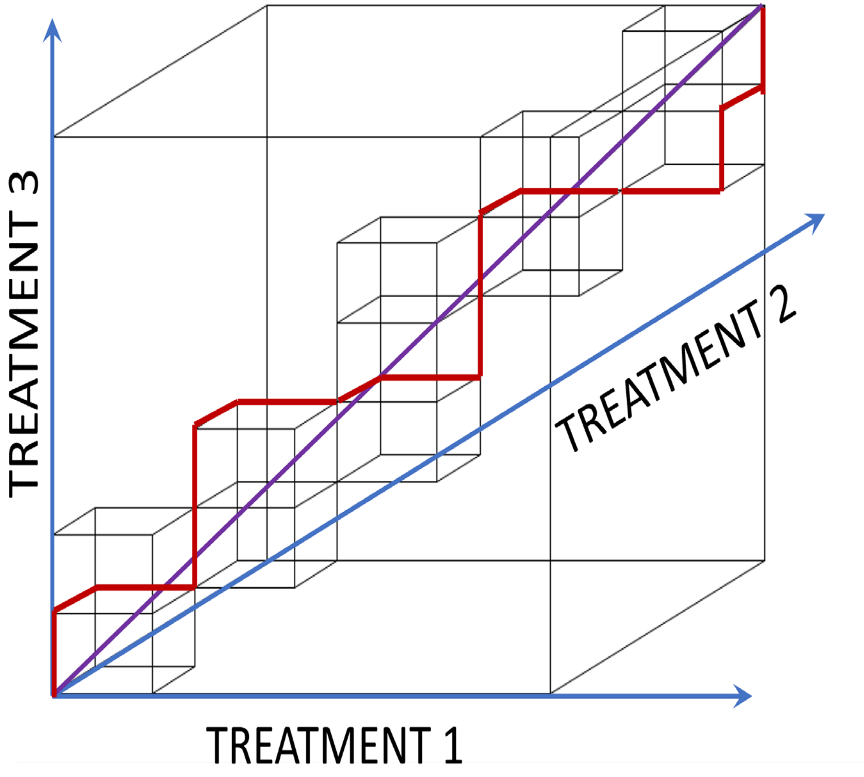
Why is the ARP Property Important?

- Variations in the unconditional allocation ratio are undesirable:
  - Provide potential for selection and evaluation bias even in double-blind studies
    - If it is known that subject randomized second has higher than average chance to receive Active treatment, a subject with better prognosis can be selected for the second slot
  - Provide a potential for accidental bias
    - in particular, in multi-center studies with randomization stratified by center – as was the case in Proschan et al. example.
  - Lead to a shift in the re-randomization distribution [Proschan et al. 2011, Kuznetsova and Tymofyeyev 2012]
    - Lowers the power of re-randomization test
- ARP violation is a common problem with the expansions of fixed and dynamic allocation procedures to unequal allocation
  - Need to be watchful!
  - For a dynamic covariate-adaptive allocation ARP requirement is that the unconditional AR is preserved for a sequence of covariates observed in the trial
- ARP property required for some theoretical results regarding the inference
  - Ye and Shao (2020) and more

Any multi-arm equal allocation procedure can be expanded to an ARP Unequal Allocation Procedure Through Mapping [K&T, 2012]

- To execute an ARP allocation to $K \geq 2$ treatment groups $G_{1,} \dots , G_K$ in $C_1: \dots :C_K$ ratio ($S = C_1 + \dots + C_K$), where C_i are integers:
  1. Execute equal allocation to S "fake" treatment arms $F_1, \dots , F_s$ following the equal allocation procedure
  2. Map groups of “fake” treatment arms to the actual treatment arms:
     - first C_1 "fake" treatment arms are mapped to G_1
     - next C_2 "fake" treatment arms are mapped to G_2 …
     - last C_K "fake" treatment arms are mapped to G_k.
- Due to symmetry with respect to fake treatment arms $F_1, \dots , F_s$, such procedure provides $C_1: \dots : C_K$ unconditional allocation ratio to actual treatment groups at every allocation
- Examples of procedures obtained through mapping: Permuted Block Design, Block Urn Design by Zhao and Weng, Drop-the-Loser Urn Design by Ivanova, expansions of minimization and other dynamic procedures by K&T
- Problem: when C_i are large integers, the allocation space is wide (wider than for PBD) and an allocation sequence can deviate a lot from the target allocation ratio
  - Need other approaches in this case

ARP with Narrow Allocation Space: Brick Tunnel Randomization [K&T 2011] – 3-arm Example



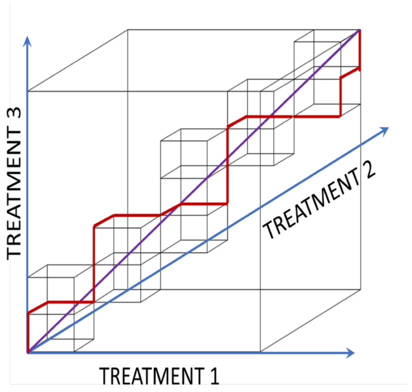
Allocation sequence:

3,2,1,3,3,2,1,2,1,3,3,2,1,1,3,2,3

- FDA Draft Guidance on master protocols recommends 1:1:$\sqrt{2}$ randomization when two treatment are compared to the same control for efficiency
  - Can be approximated with 5:5:7 ratio for illustration
- An allocation path (red line) can be depicted on a 3-dimensional unitary grid
  - A step along the Treatment *i* axis depicts the allocation to Treatment *i*
- With PB allocation, all allocation paths within the 5×5×7 block are possible
  - Observed AR can be far from the target AR for small segments
- BTR allows only the allocation paths that are contained in the sequence of unitary cubes pierced by the diagonal of the block
  - Observed AR is always close to the target AR
- Conditional probabilities are derived to keep ARP property
  - Works with irrational allocation ratio too

When and How the Brick Tunnel Randomization Can Be Used

- Whenever weird allocation ratio with large block size needs to be implemented
  - Based on efficiency considerations
  - In platform trials, where arms enter and exit
  - To keep close to the target AR with small cohorts
    - Response-adaptive allocation
    - Dose-ranging cohorts



- For 2 arms BTR is uniquely defined
  - Not always unique for 3 arms but can stick to the algorithm in Kuznetsova 2015
- SAS code for 2 and 3 arms available at the website of Sverdlov, O. (2015). Modern Adaptive Randomized Clinical Trials: Statistical and Practical Aspects - under ‘Downloads/Updates’ tab at

https://www.crcpress.com/Modern-Adaptive-Randomized-Clinical-Trials-Statistical-and-Practical-Aspects/Sverdlov/9781482239881

- R-code for >2 arms exists - to be made available

Existing ARP Expansions Not Based on Mapping

- 2-arm MTI expansions: Wide Brick Tunnel by Kuznetsova and Tymofyeyev (2014, 2015)
  - Fills in the strip $|N_{Bi} - N_{Ai} \times C_2/C_1| \leq b$ in 2-dimensional grid
  - 2 versions
- 2-arm expansions of biased coin by Kuznetsova and Plamadeala Johnson (2017)
  - The same approach in theory could be applied to minimization, but was not yet implemented (computationally intense)

Unequal Allocation Procedures That Lack ARP Property (FYI)

- Urn design described by Rosenberger and Lachin
- Expansion of the maximal procedure by Salama et al.
- Biased coin randomization and minimization expansion by Han et al.
- Doubly adaptive biased coin design procedure by Hu and Zhang applied to fixed unequal allocation as described by Sverdlov and Zhang,
- Minimum quadratic distance constrained balance randomization by Titterington
- Adaptation of biased coin randomization by Frane
- Generalized method for adaptive randomization by Russel et al.
- Generalized multidimensional dynamic allocation method by Lebowitsch et al.
- Many other procedures

What is Missing Among the ARP Randomization Tools?

- Multi-arm ARP procedures not based on mapping
  - They can be developed for the beauty of it
- Also, given the challenges, we might want to focus further development on the needs that are not met by existing procedures
- In particular, dynamic covariate-adaptive allocation with inconvenient allocation ratio in small cohorts
  - As in platform trials or response-adaptive cohort allocation
- Also, there is a question of trade-off: if a procedure has small variations in the unconditional allocation ratio, but there is no ARP alternative that meets other study needs, can we use it?
  - If yes, should the data be analyzed by re-randomization test that adjusts for variations in the unconditional allocation ratio [Han et al. 2023]?
- There is a lot to explore …

THANK YOU FOR YOUR ATTENTION!

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