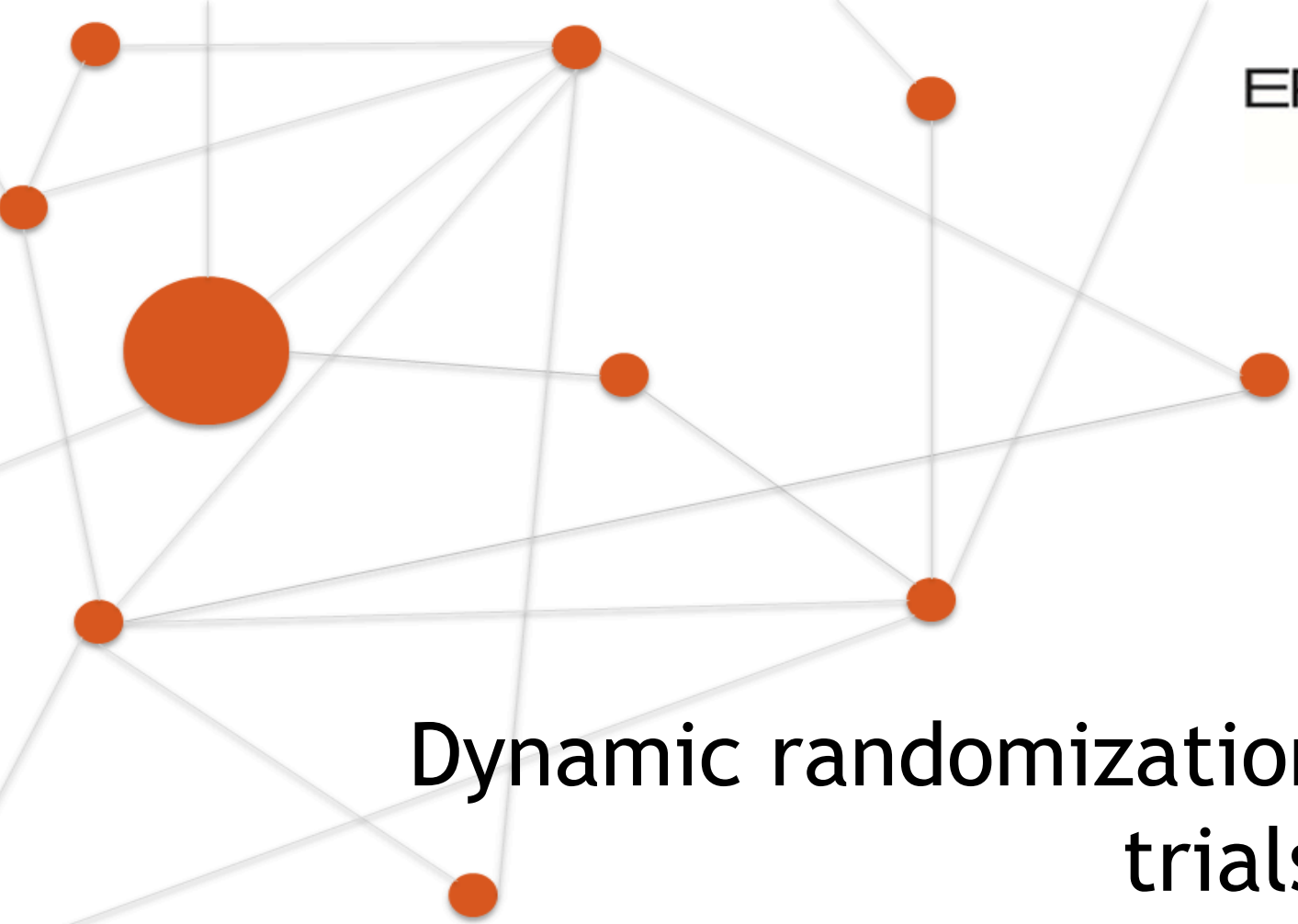

Dynamic randomization in clinical trials – a review

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Trigger for this presentation

- The ICH support the use of dynamic allocation, and the CONSORT statement declares

"trials that use minimization are considered methodologically equivalent to randomized trials, even when a randomization element is not incorporated"

- Application of Minimization in clinical trials is still less than 2% of clinical trials. (2011)

- Further education for clinicians regarding dynamic allocation techniques and instruction on their smooth incorporation into clinical studies may be beneficial.- Kimberly Fernandes Nov 16, 2005

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The basics: or the why part

Randomization

- To have valid statistical conclusions
- To eliminate biases that may affect the assessment of the results of the trial
- The distribution of known and unknown factors that may influence patient outcome should be same across the treatment groups.

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Broad classification

- Static
  - Predefined and unchanged
  - Do not use information on patients that are already in the trial.
  - For small trials with many stratification factors randomization will not insure balance.

- Dynamic
  - Not pre-defined
  - Depend on prior patient information
  - Only the first subject's group assignment is truly chosen at random

Why Dynamic?

- Treatment balance "required" within each level of stratification factors.

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Types of Randomization

- Static Randomization
  - Simple Randomization
  - Permuted Block Randomization
  - Stratified Block Randomization

- Dynamic (adaptive) randomization
  - Biased coin randomization - Efron (1971)
    - Urns method
  - The covariate-adaptive algorithms
    - Minimization
      - Tave's method (1974)
      - Pocock and Simon method (1975)
      - Frane's method
  - Dynamic balancing randomization (DBR)- Signorini et al
  - Response-adaptive randomization
  - Atkinson's DA-Optimality method
  - Zelen's method, minimization urns designs, optimal allocation techniques

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Biased coin randomization

- Efron in 1971
- Method for adjustment of assigning probabilities
- Steps:
  - Simple randomization
  - Adjust when the disparity reaches a pre-specified limit.
  - Group with the least subjects will have high probability of assignment.
  - If balance is achieved, the next subject is randomized to any of the groups with equal probability

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Urns method - adaptive biased coin approach

- Drawing balls labeled A or B from an urn, with replacement.
- For the first patient, the urn contains m balls of each type (A and B). The first patient is assigned on the basis of a random draw.
- If the assigned treatment “fails,” a ball of the other type is added to the urn. The next patient therefore has a higher probability of receiving the other treatment.
- If the assigned treatment “succeeds,” a ball of the same type is added to the urn. Thus, the next patient has a higher probability of receiving the same treatment.

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Urns method - adaptive biased coin approach

- The most widely studied member of the family of adaptive biased-coin designs
- Less affected by selection bias vs permuted-block randomization methods
- Compromise between designs that yield perfect balance in treatment assignments and complete randomization which eliminates experimental bias.
- Forces a small-sized trial to be balanced and approaches complete randomization as the size of the trial (n) increases.

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Minimization (Covariate-adaptive randomization)

- Taves and by Pocock & Simon
- A balance function that is minimized by assigning the new patient to a certain treatment.
- Imbalance score is computed based on characteristics, treatment assignment of current and enrolled patients. The patient is assigned to the treatment with the lowest imbalance score.
- Stratification considers the combinations of factor levels as mutually exclusive groups whereas minimization considers important prognostic factors together
- Minimization could be complete or partial.

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Example: Minimization

- In a trial of chemotherapy for breast cancer, with stratification factors of clinic site, estrogen receptor status (ER+ or ER-) and menopausal status

Characteristic	Trt A	Trt B
Site 1	7	8
Site 2	10	9
ER+	5	6
ER-	12	11
Pre-menopausal	8	9
Post-menopausal	9	8
Total	17	17

- Patient no: 35 = Site 2, ER+, Post-menopausal
- Subtotal for Trt A: 10+5+9 = 24; Subtotal for Trt B: 9+6+8 = 23
- So allocate to Trt B

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Tave's method

Control group

		Sex		
		Male	Female	Marginal total
Body mass index	Underweight	1	0	1
	Normal	1	1	2
	Overweight	0	1	1
	Marginal total	2	2	4

Treatment group

		Sex		
		Male	Female	Marginal total
Body mass index	Underweight	1	1	2
	Normal	1	1	2
	Overweight	1	0	1
	Marginal total	3	2	5

- 10th subject = male and underweight,

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Pocock and Simon method

- Temporarily assign to the control group,
  - Marginal totals of 3 for male and 2 for underweight category;
- Calculate the absolute difference between control and treatment
  - (males: 3 control – 3 treatment = 0; underweight: 2 control – 2 treatment = 0) and sum (0 + 0 = 0);
- Temporarily assign to the treatment group
  - so marginal totals of 4 for male and 3 for underweight category;
- Repeat step 2:
  - (males: 2 control – 4 treatment = 2; underweight: 1 control – 3 treatment = 2) and sum (2 + 2 = 4);
- Assign the 10th subject to the control group because of the lowest sum of absolute differences (0 < 4).

- Also suggested using a variance approach. this approach calculates the variance among treatment groups.

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Frane's method

- Use *P* values to identify imbalance among treatment groups: a smaller *P* value represents more imbalance among treatment groups.

- Steps
  - Temporarily assign the subject to both the control and treatment groups;
  - Calculating *P* values for each of the covariates using a *t* test or Chi-square test
  - Determine the minimum *P* value for each control or treatment group
  - Assigning the subject to the group with the larger minimum P value

- The higher minimum *P* value (1.0 > 0.317), indicates better balance is the control group

- Controls quantitative covariates in addition to categorical ones

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Dynamic balancing randomization

- Proposed by Signorini et al
- Tree-based method allowing different levels of imbalance in different strata which ensures a balance for each level of prognostic risk factors (conditional balance) whilst at the same time preserving randomness.
- Eg: 2 strata 2 levels; Gender, age groups in the order. DBR attempts to check treatment imbalance within gender first and then age groups and then the overall.
- No guarantee that balance will be achieved across the different levels for each stratum(marginal)

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Response-adaptive randomization

- also known as outcome-adaptive randomization
- Advantage of assigning fewer patients to inferior treatment
- More ethical
- Balancing is a concern again.

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Measures of performance to provide comparisons between the approaches

- A loss function-
  - interpreted as squared norm of the imbalance vector.
  - A global imbalance measure

- A forcing index- conveys the degree of randomness.

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Implementation Challenges

Three types of errors:

- Errors by investigators;
  - Patient classified to wrong strata
  - Incorrect treatment administered (assigns wrong kit or incorrect treatment admin)
- Errors in the algorithm;
  - Algorithm is not tested using simulations
- Errors caused by a faulty drug supply method.
  - Inadequate supply of study drug at site.
  - Not all study drugs are available at site

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Conclusion

- The decision about which method to use for allocating patients should be given as much consideration as other aspects of a clinical trial. Appropriately choosing between methods can affect the statistical tests required and what inferences are possible, while affecting the trial credibility. - G.R Pond 2011 May 24, British Journal of cancer,

- Minimization should be the method of choice in assigning subjects in all clinical trials. – Taves DR, 2010 –Contemp Clin Trials, 2010 Mar 31(2):180-4

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THANK YOU

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