Built to Adapt

Almac Clinical Technologies

Covariate Adaptive (Dynamic) Randomization

Presented to Gilead by Almac Biostats:

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IXRS® 3 INTERACTIVE RESPONSE TECHNOLOGY

IXRS 3 Simplify

IXRS 3 Simplify PLUS

IXRS 3 UNLIMITED

CAR Methodologies

ICH E9:

- "The use of a dynamic allocation procedure may help to achieve balance across a number of stratifying factors simultaneously provided the rest of the trial procedures can be adjusted to accommodate an approach of this type."
- "Dynamic allocation is an alternative procedure in which the allocation of treatment to a subject is influenced by the current balance of allocated treatments and, in a stratified trial, by the stratum to which the subject belongs and the balance within that stratum."

Almac Biostats:

- In other words, there is no Stratified List that will tell you the 1st, 2nd, 3rd,… treatment assignment.
- Treatment assignments will be made dynamically via an algorithm.

CAR Considerations

EMA: Points to Consider on Adjustment for Baselines Covariates (2003)
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003639.pdf:

- **I.3.** *"…such methods remain highly controversial. Thus, applicants are strongly advised to avoid such methods. If they are used, the reasons should be justified on solid clinical and statistical grounds."*
- **II.4.** *"Dynamic allocation is strongly discouraged… Applicants will be required to describe the sensitivity analyses they intend to perform to support the conclusions from the primary analysis. Without adequate and supporting/sensitivity analyses, an application is unlikely to be successful."*

To use CAR, the following 2 areas of justification is required:

1. **Clinical Justification:**
   - All stratification factors used are clinically justified
   - Evidence / reasoning of why there could be statistical differences across the levels (e.g. science suggests that potential differences exist across the stratification factor levels because…)
2. **Statistical Justification:**
   - Given the number of Stratification Factors, Sample Size and Treatment Ratio;
   - Treatment Balance can only be achieved through a dynamic allocation method VERSUS
   - Standard list-based randomization method (where balance would be compromised).
   - *Simulations are often required to provide / prove Statistical Justification.*

CAR Considerations (continued)

EMA: Guideline on adjustment for baseline covariates in clinical trials (2015), Section 4.2:
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/03/WC500184923.pdf –

- *"… The (simplified) idea behind dynamic allocation is to measure the imbalance marginally over each prognostic factor and to minimize e.g. the (weighted) sum of imbalances over all prognostic factors, thus maximising overall balance. However, dynamic allocation does not guarantee balance within combinations of prognostic factors. Deterministic schemes should be avoided."*
- *"Possible implications of dynamic allocation methods on the analysis e.g. with regard to bias and Type I error control should be carefully considered, taking into account that for some situations (e.g. planned unbalanced treatment allocation that allows to change the allocation ratio at every allocation) it has been shown that in case of dynamic treatment allocation conventional statistical methods do not always control the Type I error. To properly account for such problems the use of re-randomisation methods in the analysis should be considered."*

Key Points:

- CAR balances within Factor Levels, but does not guarantee Stratum Level (cross-combination) balance
- Standard Blocked Randomization would balance within the cross-combination Stratum Levels
- CAR algorithm should have an appropriate Random Component (e.g. biased coin probability value < .90)
- Biased coin probability value = 0.90 is akin to Block Size = 2 for Blocked Rand List; not recommended due to predictability
- If using CAR, you should be prepared to do re-randomization at the end of the study to prove Type I error did not occur
- Re-randomization typically not required for Standard Blocked Randomization

Parameterization Notes

- Treatment Codes / Ratios
- Balance Factors & Levels (Stratification)
  - STUDY an optional factor that provides additional protection to maintaining Study level balance
    - May not be needed if other factors have low number of levels
  - SITE: Trending away from using SITE as a balancing factor
    - Standard of Care may be similar across SITEs within the same Country / Region
    - May not be feasible given Covid-19 climate (where Site transfers are common)
    - Consider using Region or Country (more clinically meaningful, stable, consistent across study duration)
- Factor Weights: can be applied to each factor according to the importance of obtaining treatment balance
- Treatment Assignment Probability (p)
  - Biased-coin probability value (common values = 0.70, 0.75, 0.80, 0.85)
  - In case of TIE, assign according to allocation ratio
  - General rule: select the lowest value that provides the required treatment balance (to avoid predictability)

Minimization (Pocock & Simon, 1975) Algorithm Example

Current Status: 49 Subjects enrolled (25xA, 24xB)

Factor	Level	Trt A	Trt B	Total
Site	1	5	5	10
	2	11	10	21
	3	9	9	18
Gender	M	13	11	24
	F	12	13	25
Symptom Score	1	5	4	9
	2	13	15	28
	>=3	7	5	12
Study	All	25	24	49

Minimization Algorithm Example (Continued)

New subject (50th) to be randomized into study: SITE=2, GENDER=M, SYMPTOMS SCORE=2

Factor	Level	Trt A	Trt B	Total
Site	1	5	5	10
	2	**11**	**10**	**21**
	3	9	9	18
Gender	**M**	**13**	**11**	**24**
	F	12	13	25
Symptom Score	1	5	4	9
	2	**13**	**15**	**28**
	>=3	7	5	12
Study	**All**	**25**	**24**	**49**

Minimization Algorithm Example (Continued)

Step 1. Calculate imbalance assuming new subject is randomized to Trt A

Factor	Level	Trt A	Trt B	Diff
Site	1	5	5	
	2	**11 + 1**	**10**	**Diff(12,10) = 2**
	3	9	9	
Gender	**M**	**13 + 1**	**11**	**Diff(14,11) = 3**
	F	12	13	
Symptom Score	1	5	4	
	2	**13 + 1**	**15**	**Diff(14,15) = 1**
	>=3	7	5	
Study	**All**	**25 + 1**	**24**	**Diff(26,24) = 2**
			Total Imbalance A	**8**

Minimization Algorithm Example (Continued)

Step 2. Calculate imbalance assuming new subject is randomized to Trt B

Factor	Level	Trt A	Trt B	Diff
Site	1	5	5	
	2	**11**	**10 + 1**	**Diff(11,11) = 0**
	3	9	9	
Gender	**M**	**13**	**11 + 1**	**Diff(13,12) = 1**
	F	12	13	
Symptom Score	1	5	4	
	2	**13**	**15 + 1**	**Diff(13,16) = 3**
	>=3	7	5	
Study	**All**	**25**	**24 + 1**	**Diff(25,25) = 0**
			Total Imbalance B	**4**

Minimization Algorithm Example (Continued)

Step 3. Determine which treatment will minimize the current imbalance

Factor	Level	Trt A	Trt B	Imbalance	
Site	1	5	5	A	B
	2	**11**	**10**	**2**	**0**
	3	9	9		
Gender	**M**	**13**	**11**	**3**	**1**
	F	12	13		
Symptom Score	1	5	4		
	2	**13**	**15**	**1**	**3**
	>=3	7	5		
Study	**All**	**25**	**24**	**2**	**0**
			Total Imbalances A, B	**8**	**4**

Minimization Algorithm Example (Continued)

Step 4. Determine Treatment Assignment Probabilities

(Assign B with p=0.80; Assign A with p=0.20)

	Treatment Assignment Probabilities [associated random number range to be utilized by the IXRS]	
	Trt A	**Trt B**
Minimum Imbalance: 1 arm		
Min. Imbalance = Trt A	p= 0.80 [0.00001-0.80000]	p= 0.20 [0.80001-0.99999]
Min. Imbalance = Trt B	**p= 0.20 [0.80001-0.99999]**	**p= 0.80 [0.00001-0.80000]**
Minimum Imbalance: 2 arms		
Min. Imbalance = Trt A, Trt B	p= 0.50 [0.00001-0.50000]	p= 0.50 [0.50001-0.99999]

Minimization Algorithm Example (Continued)

Step 5. Assign next available Random Number

- **Compare Assigned Rand_No against the Step 4 Probabilities**

Assign Treatment:

- 0.00001<= Rand_No <= 0.80000: assign **Treatment B**
- 0.80001<= Rand_No <= 0.99999: assign **Treatment A**

TrialID,Seq_NO,Rand_NO
Protocol,1001,0.73902
Protocol,1002,0.27248
Protocol,1003,0.70953
Protocol,1004,0.31916
Protocol,1005,0.36785
Protocol,1006,0.10449
Protocol,1007,0.03680
Protocol,1008,0.53333
Protocol,1009,0.37130
Protocol,1010,0.04019
Protocol,1011,0.79345
Protocol,1012,0.95910
Protocol,1013,0.64804
Protocol,1014,0.33911
Protocol,1015,0.33736
Protocol,1016,0.37804
Protocol,1017,0.56103
Protocol,1018,0.95252
Protocol,1019,0.48285
Protocol,1020,0.71221

CAR Key Highlights

- Almac conducts preliminary sims to provide statistical justification and help determine parameters
- Separate Almac document (from IXRS requirements document(s)):
  - CARURS: Covariate Adaptive Randomization User Requirements Specification
  - CARURS Approvers (only person(s) permitted to know details of CAR algorithm)
- Random Numbers List (for probabilistic treatment arm assignment)
- Handling of Special Cases (mis-stratification; randomized in error; site transfers)
- CAR Validation Process
- Extended timelines for Development and Testing of the adaptive randomization algorithm
- Potential need to plan for re-randomization tests to check for Type I Error at the end of study

Questions?