Dynamic allocation

How to stratify if you must……..

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Dynamic Allocation: Balancing Act

- Some anecdotal history
- Some issues and a model
- Evalution
- And now…..

Anecdotal history

PtC on Adjustment for Baseline Covariates final versus draft

"Achieving Balance in Clinical Trials. An unbalanced view from EU regulators." Buyse & McEntegart. ACT, May 04.

"In our view, the CPMP's position is unfair, unfounded, and unwise."

"Achieving Balance in Clinical Trials." Day, Grouin, Lewis. ACT, Jan 05.

" To say the guidance does not cite any references to support its views is an irrelevant argument."

"If B's and M's criticism were to be "fair", then on this basis they would also have to reject all the advice written in regulatory guidance with which they do agree."

Randomisation

- The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias (ICH).
- "…having used a random allocation, the sternest critic is unable to say when we eventually dash into print that quite probably the groups were differentially biased through our predilections or through our stupidity."
- Generation of allocation sequences

Dynamic allocation

Covariate adaptive allocation

Variable	Category	Group A		Group B		New
Sex	Male	4	**5**	5	**6**	*
	Female		4		4	
BMI	< 30	4	**5**	3	**4**	*
	≥ 30	4		6		
Fasting Chol	≤ 6.0	5		7		
	> 6.0	3	**4**	2	**3**	*
Total allocated		8		9		

New -> A Diff = |5-5| + |5-3| + |4-2| = **4**

New -> B Diff = |4-6| + |4-4| + |3-3| = **2**

Random element: probability of assignment *p*

Dynamic allocation

How to stratify if you must…….

Dynamic allocation vs Stratified Blocks

(where simple randomisation may do the trick as well)

Randomisation based inference

Two samples:

$X_1, X_2,...,X_m$ and $Y_{m+1}, Y_2, ..,Y_{m+n}$

$X_i = u_i + V_i$, $Y_i = u_i + V_i$ u_i is associated with the i-th subject

$E(X_i) = u_i + \xi$, $E(Y_i) = u_i + \eta$ V_i with drug & circumstances

Subjects (represented by u_i) do not constitute a random sample

Impossible to distinguish between the $H_0 : \xi - \eta = 0$ and $H_A : \xi - \eta \neq 0$

Randomisation of the subjects -> *Randomisation* of the u_i's

Tested most powerfully by means of a *permutation test*

T-test is *a large sample approximation*.

(inference is over all possible permutations……..)

Roes, Pharmaceutical Statistics 2004, 187-191

Dynamic allocation ?

$X_1, X_2,..,X_m$ and $Y_{m+1}, Y_2, ..,Y_{m+n}$

$X_i = u_i + V_i$, $Y_i = u_i + V_i$ u_i is associated with the i-th subject

$E(X_i) = u_i + \xi$, $E(Y_i) = u_i + \eta$ V_i with drug & circumstances

Allocation to treatment (u_i) in such a way that (you expect, hope):

$$Mean_{1,m}\ (u_i) = Mean_{m+1,m+n}(u_i)$$

And then, under the Gaussian assumption for V_i, the t-test is a (good approximation to) most powerful test.

Balance, size and power

Effect of covariates on size (unadjusted)

Effect of covariates and covariate adjustment on precision & bias

Pocock et al., Stats in Medicine 2002, 2917-2930.

Degree of imbalance	STR4		MIN (0.70)	
	p50	p99	p50	p99
Groups of 50	4	16	0	4
Groups of 100	6	20	2	4
Groups of 200	6	24	0	4

Hagino et al., Contr. Clin. Trials 2004, 572-584

Balance and power

Degree of imbalance in simultaneous distribution

P-values of chi-square test for 3x3 contingency table

	STR4		MIN (0.70)		SR	
	p1	p50	p1	p50	p1	p50
Groups of 200	0.22	0.87	0.11	0.86	0.01	0.47

So, interaction between covariates presents a problem.

Balance and power

Type 1 error & power (survival analysis, 200 pts, 10.000 simul.)

		MIN (1.0)	STR2	SR
H_o (1.0)	Log-rank	0.0352	0.0334	0.0505
	Stratified Log rank	0.0466	0.0446	0.0504
H_1 (1.6)	Log-rank	0.4155	0.4265	0.4302
	Stratified Log rank	0.4790	0.4904	0.4778
H_1 (2.0)	Log-rank	0.7793	0.7852	0.7610
	Stratified Log rank	0.8215	0.8303	0.8054

Allocation concealment

- Prediction of next treatment allocation
  - Small known block sizes in case of stratified randomisation
  - Known variables/parameters of dynamic allocation algorithm

- "Blind" estimation of treatment effect
  - Stratified randomisation:
    - Block size 2 -> bi-modal distribution of pairwise differences
    - Block size 4 -> similar generalization
    - Random lengths of 2 & 4: still possible

  Hence: large block sizes!

  Van der Meulen 2006

- Dynamic allocation
    - Similar options (through ancova), but less precise

And now…….

- Inference is imperfect….what's new?
- Principal method may not be the overriding concern, actual implemention could be be (also for more complicated stratified randomisation)
- Advocating transparent account of methods applied (& potential errors) more important & effective.