Minimization, permuted blocks and simple randomization

Marc Buyse, ScD
IDDI, Louvain-la-Neuve, Belgium

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In randomized clinical trials, the treatment allocation method should...

- minimize the type I error
- minimize the type II error
- balance all known and unknown prognostic factors among treatment groups (avoid accidental bias)
- minimize the predictability of treatment assignments (avoid selection bias)
- be simple and foolproof (avoid other biases)
Simulations in advanced ovarian cancer

Survival probability

Time (years)

0.00 0.25 0.50 0.75 1.00

0 0.5 1 1.5 2 2.5 3 3.5 4 4.5 5

CAP

CP
Simulations – data generation

- Patients: sampled at random (N=400), with replacement, from meta-analysis dataset
- Center: sampled at random from skewed distribution
- Time of entry: sampled at random from uniform distribution over accrual period
- Treatment: allocated using various methods (next slide)
- Survival time: unchanged under control, prolonged under treatment, with HR $= \frac{\lambda_T}{\lambda_C} = 0.8$
Simulations - allocation techniques

- Simple randomization
- Permuted blocks within strata defined by center
  - only
  - and prognostic class
  - and 1 factor (residual disease)
  - and 3 factors (same + performance status + age)
  - and 5 factors (same + histologic grade + FIGO stage)
- Minimization
  - (as permuted blocks)
Balance
Simulations – mean overall imbalances

- Simple
- PB Center
- PB Class
- PB 1
- PB 3
- PB 5
- Min Center
- Min Class
- Min 1
- Min 3
- Min 5
Simulations – mean imbalances in factor levels

- Simple
- PB Center
- PB Class
- PB 1
- PB 3
- PB 5
- Min Center
- Min Class
- Min 1
- Min 3
- Min 5
Simulations – mean imbalances in strata
Size and power
Simulations – size of logrank test
(dashed = stratified for 5 factors)
Simulations – power of logrank test
(dashed = stratified for 1 factor)
Simulations – power of logrank test
(dashed = stratified for 5 factors)
Simulations – power of logrank test
(dashed = stratified for center and all factors)
Simulations in age-related macular degeneration (AMD)

Minimization for
- Type of lesion
- Prior PDT
- Center

*Other important baseline factors*
- Size of lesion
- Vision
- Gender

R

- Sham
- Macugen 0.3 mg
- Macugen 1 mg
- Macugen 3 mg
Simulations - allocation techniques

- Simple randomization
- Permutated blocks within strata defined by
  - Type of lesion
  - Prior PDT
- Minimization on
  - Type of lesion
  - Prior PDT
  - Center
Predictability
Simulations – correctly guessed treatment allocations

- Simple global
- Simple local
- PB global
- PB local
- Min global
- Min local

%
Accidental bias
Simulations – imbalances in baseline prognostic factors
Simulations in Micro-array In Node negative Disease may Avoid ChemoTherapy (MINDACT)

Minimization for
- CG Risk
- HR Status
- Age
- Her2
- Axillary Method
- Surgery
- Center

Use Clinical-Pathological Risk
Use 70-gene Signature Risk

www.iddi.com
Simulations – worst case scenario for baseline covariate imbalances
Conclusions – desirable characteristics

- **Balance**: minimization best, especially for large numbers of factors
- **Size**: slight gains with PB or minimization (or with stratified analyses)
- **Power**: negligible gains (more gain with stratified analyses)
- **Predictability**: quite limited if guesses based on local knowledge
- **Accidental bias**: slight gains with PB or minimization
- **Simplicity**: simple randomization best
Conclusions – minimization can be recommended...

- to ensure balance over a large number of factors
- regardless of the distribution of patients in the factor levels
- in trials of large or small size
- with center as a minimization factor in double-blind trials
- without center as a minimization factor in open-label trials
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