Adaptive Randomisation
A regulator‘s view

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* Views expressed here are those of the author and do not represent those of the Paul-Ehrlich-Institute

The PtC on Adjustment for Baseline Covariates

II.4 Dynamic allocation

Dynamic allocation is ***strongly discouraged***. However, if it is used, then it is imperative that all factors used in the allocation scheme be included in the analysis. Even with this requirement, it ***remains controversial whether the analysis adequately reflects the randomisation scheme***. Applicants will be required to describe the sensitivity analyses they intend to perform to support the conclusions from the primary analysis. ***Without adequate and appropriate supporting/sensitivity analyses, an application is unlikely to be successful***. ..‘

Why Randomise?

- Balance treatment groups to all known & unknown covariates (on average)
- Minimise selection bias
- Allow for a proper statistical analysis
  $\Rightarrow$
  method of randomisation might impact the analysis method

Randomisation in CTAs and Submissions
Sometimes a ‚Black Box‘ for Regulators

Some (un-)typical(?) statements:

- Randomisation was done using IVRS by a CRO
- An adaptive randomisation procedure employing the stratification factors A, B…
- An minimisation procedure according Pocock / Simon (x) with stratification for A, B, C….

Sometimes without further information

Adaptive Randomisation

Treatment assignment of the next patient based on the patient‘s covariates in order to minimise a measure of overall covariate imbalance.

- deterministic (e.g. Traves)
- probabilistic (e.g. Pocock-Simon)

The different methods for adaptive randomisation have parameters to be specified (done more or less on an adhoc basis).

Deterministic Procedures (1)

- ‚best' overall balancing properties
- Mainly non-random treatment allocation
- Predictability
- Permutation tests only appropriate if one assumes patient entry into the study as random
- Validity of patient population models requires assumption of a homogeneous population

Deterministic Procedures (2)

How to verify that

- patient entry is a random process?
- patients are from a homogeneous population?

$\Rightarrow$ Strong regulatory concerns with deterministic procedures

Probabilistic Procedures

- ‚good' overall balancing properties
- Partially random allocation (depending on the random component)
- Appropriate tests are available (e.g. re-randomisation tests conditional on the order of patient entry into the study)
- Validity of patient population models requires assumption of a homogeneous population

How to verify that patient come from a homogeneous population?

Adaptive Randomisation - Advantages

- Requires identification of prognostic factors at the design stage
- Powerful tool to increase overall balance between treatment groups
- A larger number of prognostic factors than with a stratified randomisation can be considered

Adaptive Randomisation - Disadvantages

- Either deterministic or strong deterministic component
- Increase in logistic complexity
- Treatment balance within strata might not be optimal
- Analytical aspects

Analytical Aspects (1)

Following adaptive randomisation literature suggests:

- unadjusted (standard) tests tend to result in conservative p-values
- Covariate adjusted (standard) tests tend to ensure the Type I error

However, these findings are (mainly) based on simulations for probabilistic procedures (comparing 2 treatments)

Are they always true?

Analytical Aspects (2)

In order achieve a test of proper size, covariates used in the minimisation algorithm should be adjusted for in the analysis model.

Even following unrestricted randomisation a non-linear model for covariate adjustment (e.g. logistic regression) might result in a smaller p-value and larger variance for the effect estimate than an unadjusted analysis

Problem:
Is this effect probably increased by adaptive randomisation?

Analytical Aspects (3)

- Coverage of (conventional) confidence intervals
- Validity of subgroup analysis in case treatment allocation is depending on covariate defining the subgroup
- Has adaptive randomisation any impact on handling of drop-outs in the analysis?

Analytical Aspects (4)

- Has adaptive randomisation any impact on conventional methods to deal with multiplicity?
- Has adaptive randomisation any impact on the validity of ‚conventional' methods used in group sequential trials?
- Has adaptive randomisation any impact when dealing with design adaptations

Summary

Adaptive treatment allocation procedures (even if probabilistic) raise several questions that are still not completely solved

$\Rightarrow$

Regulators reluctant with respect to adaptive randomisation