

Minimization: A Case Study of Covariate-Adaptive Randomization

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Agenda

- Case-study: put in context
- Study design: why dynamic randomization?
- What ICH E9 states about
- Minimization algorithm: how it works & computational example
- Final treatment allocation
- Statistical Analysis
- Implementation
- To sum up

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Case-study: background

- Design: POC, double-blind, randomized, active-controlled study
- Population: ~120 preterm infants overall

A **premature infant** is a baby born before 37 completed weeks of gestation (more than 3 weeks before the due date).



- Preterm infants have surfactant deficiency resulting in most of the case in respiratory distress syndrome causing respiratory failure

Case-study: background

- In general, ensuring balance in important prognostic covariates across treatment groups is desirable for many reasons.

European Medicines Agency

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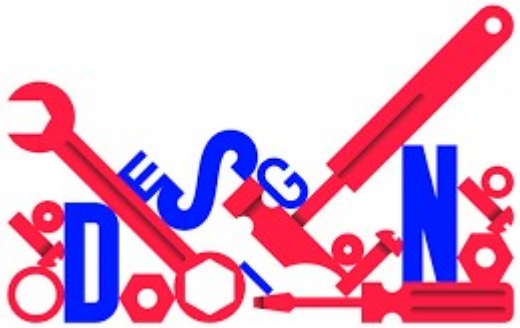
CPMP/ICH/2711/99

ICH Topic E 11
Clinical Investigation of Medicinal Products in the Paediatric Population

2.5.1 Preterm newborn infants

and other chemicals. Study design issues that should be considered include: (1) weight and age (gestational and postnatal) stratification; (2) small blood volumes (a 500-g infant has 40 mL of blood); (3) small numbers of patients at a given center and differences in care among centers; and (4) difficulties in assessing outcomes.



- Stratification Factors:
  - GA group (i.e., 24^{+0}-26^{+6}, 27^{+0}-29^{+6} wks)
  - NICU* (~ 20)

*Neonatol Intensive Care Unit

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Study design: why dynamic randomization?

Stratification using permuted blocks within strata is generally used (i.e. separate lists for each combination of factor levels)

Ensures that the overall numbers of patients in the treatment groups are balanced on prognostic factors provided that each block used is completed

When the no. of factors or strata increase but the study is small or moderate-sized,
the aim of stratification may not be achieved

Dynamic randomization method can help in ensuring the balance of the treatment groups over the selected prognostic factors

What ICH E9 states about

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CPMP/ICH/363/96

ICH Topic E 9
Statistical Principles for Clinical Trials

2.3.2 Randomisation

use of a dynamic allocation procedure (see below) may help to achieve balance across a number of stratification factors simultaneously provided the rest of the trial procedures can be adjusted to accommodate an approach of this type. Factors on which randomisation has been stratified should be accounted for later in the analysis.

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. Deterministic

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Static vs Dynamic: main differences

	Static	Dynamic
	➢ Treatment assigned using a sequence established prior to any patients entering the study	➢ Treatment allocation is determined only when the patient arrives
	➢ The treatment allocation scheme is predefined and unchanged as patients enroll onto the study	➢ Treatment is generated taking into account the stratification factor levels of each of the previously enrolled patients
	➢ Balance in factor interaction cells	➢ Balance achieved in each individual factor
As example, when balancing on gender and smoking status	▪ Males-smokers ▪ Males-non smokers ▪ Female smokers ▪ Female-non smokers	▪ Males ▪ Females ▪ Smokers ▪ Ex-smoker

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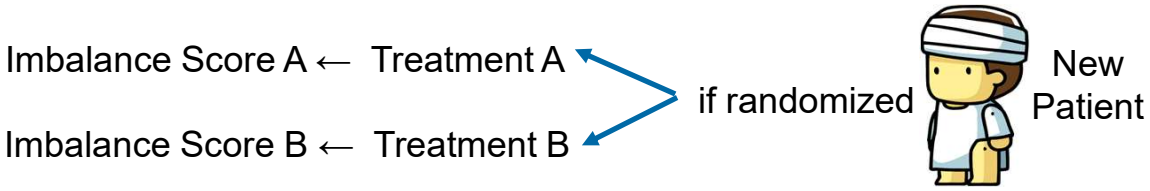
Dynamic randomization: minimization

- Minimization, pioneered by Taves (1974) and expanded by Pocock and Simon (1975), is one of commonly used “covariate-adaptive” allocation procedure
- Based on stratification factor levels of patients currently on the trial and the treatments each of them is assigned, an imbalance score is computed for each available treatment
- This imbalance score represents the imbalance that would be generated across treatments taking into account stratification factors levels if that treatment was assigned



- The treatment with the lowest imbalance score is then given preference when assigning treatments

Dynamic randomization: minimization (con't)

- The imbalance score is a **summary measure of the lack of balance** created by the potential treatment k assignment

$$G_k = \sum_{i=1}^{M} w_i d_{ik},$$

where w_i are weights chosen depending on which covariates are deemed of greater importance.

- The **distance measure** is a way of measuring how far the potential treatment allocation is from the 'ideal' allocation and can be measured in different ways:
  - **RANGE** of the differences
  - **VARIANCE** of the differences
  - **UPPER LIMIT OF ACCEPTABLE TREATMENT IMBALANCE**
  - **SIGN RULE**

Dynamic randomization: minimization (con't)

- The treatment will be assigned according to the following set of probabilities:

  prob(T=k)=p_k where $p_1 \geq p_2 \geq p_3 \geq \ldots \geq p_n$ and $\sum p_k = 1$

- p_k can be a fixed number or a function of G_k

- There is no obvious decision rule for optimizing one's choice of pk:
  - if p_1=1, the chance of treatment imbalance is minimized but predictability is at maximum
  - If p_1 tends to 1/ No. of Treatments the reverse is true.

Dynamic randomization: minimization (con't)

- The Pocock-Simon algorithm extends the Taves one by introducing a random element to each allocation step

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2.3.2 Randomisation

the stratum to which the subject belongs and the balance within that stratum. Deterministic dynamic allocation procedures should be avoided and an appropriate element of randomisation should be incorporated for each treatment allocation. Every effort should be made to retain the double-blind status of the trial. For example, knowledge of the treatment

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Example

- Distribution by treatment of the first 40 randomized patients by stratification factors (Site and GA group)

	Treatment Group		
Site	Tested	SOC	Total
101	1	2	3
102	1	3	4
103	0	1	1
104	0	1	1
105	1	0	1
106	0	1	1
108	1	1	2
109	2	0	2
110	2	1	3
111	2	0	2
112	1	1	2
113	2	1	3
114	0	1	1
115	2	1	3
116	3	2	5
117	1	1	2
118	1	2	3
120	0	1	1
Total	20	20	40

	Treatment Group		
GA	Tested	SOC	Total
<27 week	9	7	16
>=27 week	11	13	24
Total	20	20	40

- 41st infant with **GA 26+3** week is randomized at **Site 115**

- Ideal allocation Site: 3*1/2=1.5
- Ideal allocation GA: 16*1/2=8

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Example: score computation

Tested treatment

	Treatment Group		
Site	Tested	SOC	Total
…	…	….	….
115	3-1.5=1.5	1-1.5=0.5	4
…	..	…	….
Total	21	20	41

If assigned to

SOC

	Treatment Group		
Site	Tested	SOC	Total
…	…	….	….
115	2-1.5=0.5	2-1.5=0.5	4
…	…	….	….
Total	20	21	41

Var: $(1.5)^2/2 + (0.5)^2/2 = 1.25$

Var: $(0.5)^2/2 + (0.5)^2/2 = 0.25$

Imbalance score: **0.75**

GA	Treatment Group		
Frequency	Tested	SOC	Total
<27 week	10-8=2	7-8=-1	17
>=27 week	11	13	24
Total	21	20	41

Imbalance score: **3.75**

GA	Treatment Group		
Frequency	Tested	SOC	Total
<27 week	9-8=1	8-8=0	17
>=27 week	11	13	24
Total	20	21	41

Var: $(2)^2/2 + (-1)^2/2 = 2.5$

Var: $(1)^2/2 + (0)^2/2 = 0.5$

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Example: treatment selection

- Treatment with the lowest imbalance score is chosen with the highest probability (i.e., 80%)
- A random number is generated by the system to assign the treatment

MinimisationReportID	Patient Code	NICU	GA group	TotalImbalance_TEST1	TotalImbalance_SOC1	Probability_TEST1	Probability_SOC1	RandomNumber	RejectedTrtGroupID	Treatment Group
31	116004	116	2	1,75	0,75		80	59,81374232	N/A	SOC
32	116005	116	2	0,75	1,75	80		89,79997239	N/A	TEST
33	118003	118	2	1	1	50	50	78,34162441	N/A	SOC
34	112002	112	1	3,75	0,75		80	83,24530515	N/A	SOC
35	113003	113	1	1,75	0,75	100		7,667459877	SOC	TEST
36	111002	111	2	1,5	1,5	50	50	12,57114062	N/A	TEST
37	101003	101	2	1	1	50	50	62,07584467	N/A	SOC
38	120001	120	2	0,75	1,75		100	11,58054872	TEST	SOC
39	110003	110	2	1	3	80		61,08525277	N/A	TEST
40	115003	115	2	2,75	1,75		80	49,6269048	N/A	SOC
41	115004	115	1	3,75	0,75		80	35,01211155	N/A	SOC
42	111003	111	2	3	3	50	50	68,15478688	N/A	SOC
43	101004	101	2	1,5	5,5	80		53,53999364	N/A	TEST
44	114002	114	1	1,5	1,5	50	50	22,56317168	N/A	TEST
45	104002	104	2	0,75	3,75		100	7,948378431	TEST	SOC
46	101005	101	2	1,75	4,75		100	12,85205917	TEST	SOC

Treatment with highest imbalance score are randomly chosen

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Final treatment allocation

- Finally, 123 infants were randomized in 17 sites
- Overall, 52% were randomized in the tested treatment arm

> Of note: no factor to balance the total number of subjects entering each of the treatment groups was included in the algorithm

- At factor levels

	Frequency	%
Balanced	5	26.3
1 infant, Odd number	9	47.4
2 infants	1	5.3
>2 infants	4	21.0

Statistical analyses

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dynamic allocation procedure (see below) may help to achieve balance across a number of stratification factors simultaneously, provided the rest of the trial procedures can be adjusted to accommodate an approach of this type. Factors on which randomization has been stratified should be accounted for later in the analysis.

- Stratification factors were included in main efficacy analyses

As example, FiO_2 over 24 hr post-treatment was analyzed using MMRM including treatment, time point, treatment by time point interaction, NICU and GA group as fixed effects and pre-dose FiO_2 as covariate

Implementation

- Implemented through a central system (i.e., Interactive Response Technology)

  CRO system was used in our study:
  ClinPhone Randomisation and Trial Supply Management (RTSM)

- System must be validated and meet applicable regulatory requirements

- Its should be used by fully trained staff and its use should be documented with standard operating procedures

- Details on algorithm computation included in the randomization specification document

Implementation

- UAT script customized to test the algorithm:
  - Randomization of a set of patients
  - Check of imbalance score calculation
  - Check of patient treatment assignment

In case of any deviation, UAT issue log was released, system adapted and tested again

ID	Requirement # & Description	Testing Procedure	Expected Results	Actual Result	Pass / Fail
1.	2 Randomisation	Open the Minimisation report and take a screen print 1. Screen and randomise 10 patients at site 101, taking a screen print of each randomisation visit response 2. Screen and randomise 5 patients at site 102, taking a screen print of each randomisation visit response 3. Screen and randomise 8 patients at site 103, taking a screen print of each randomisation visit response 4. Screen and randomise 6 patients at site 104, taking a screen print of each randomisation visit response 5. Screen and randomise 9 patients at site 105, taking a screen print of each randomisation visit response	A screen print is taken of the report showing no patients have been randomised (SQL error: Invalid object name 'MinimisationReport') 1. 10 patients at site 101 have been randomised and screen prints are taken to show the randomisations 2. 5 patients at site 102 have been randomised and screen prints are taken to show the randomisations 3. 8 patients at site 103 have been randomised and screen prints are taken to show the randomisations 4. 6 patients at site 104 have been randomised and screen prints are taken to show the randomisations 5. 9 patients at site 105 have been randomised and screen prints are taken to show the randomisations	s Expected ☐ Deviation From Expected Result ☒ Record deviations on the SQ ... e Log SQ Issue ID 1 _____	Pass ☐ Fail ☒ Not Run ☐

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To sum up

- Dynamic randomization can be considered an alternative to simple or permuted blocks randomization method for small to moderate-sized clinical trials with many factor levels
- Modern technologies readily enable its implementation requiring more efforts during the setup phase…

BUT

select the appropriate provider!

- Guideline allows for its use: no request for information was received during protocol submission by Regulatory Authorities

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