Use of the Minimization Technique: History and Experience of the EORTC

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EORTC

EUROPEAN ORGANISATION for RESEARCH and TREATMENT of CANCER

Aim: To conduct, develop, coordinate research in Europe on treatment of cancer and related problems

EORTC

- 22 Clinical Research Groups: network of more than 200 institutions from 31 different countries
- +/- 2,000 collaborators (clinicians, pathologists, researchers,....)
- More than 5,000 patients are entered into EORTC trials each year (database of more than 140,000 patients)
- 30,000 patients being followed-up
- +/- 80 phase I, II and III trials open to patient entry (80% are randomized)

EORTC Data Center

- Established in 1974
- 130 staff members: Stat, MD, DM, IT, admin
- Ensures from an independent, academic point of view the highest possible quality of trials
  - Design
  - Conduct
  - Analysis
  - Publication

EORTC Data Center

1974

- **Central randomization with random <u>permuted blocks</u> within strata**
- **Problems:**
  - **Practical implementation: pen and paper**
  - **Blocks: imbalance due to unfilled blocks**
- **Need for a more pragmatic method**

Randomization History

During the early 80s:

Permutation blocks

Minimization

First on Apple II
Later on mainframe server

Minimization Technique

- Original paper by Pocock and Simon (1975)
- Extension by Freedman and White (1976)

Many options available

- **Dynamic/adaptive:**
  Assignment depends on the covariates of the patients already enrolled
- **Minimize:**
  Allocation so that it minimizes some measure of variance or efficiency

Minimization at the EORTC

Algorithm based on Freedman and White 1976:

- **minimize $\sum$variance**
- **choose at random between all "eligible" treatments**

Treatment is eligible

$\Updownarrow$

Allocation to this treatment $\rightarrow$ imbalance $\leq d$

Minimization at the EORTC

N treatments **M stratification factors**

If a new patient enters the trial

For each treatment:

- $G_k = \sum^M$(# pts with identical stratification level)
- *Pr*(new trt = k) =

$$\begin{cases} 1/L & \textit{if} \quad (G_k - \min(G_i)) \leq d;\ k = 1, \ldots, L \\ 0 & \textit{if} \quad \text{otherwise} \end{cases}$$

Minimization at the EORTC

Stratification F

- **gender**
- **age**
- **institution**

Study entry

Gender:	Arm A = **55** males ↔ Arm B = **56** males
Age:	Arm A = **32** > 60 yrs ↔ Arm B = **37** > 60 yrs
Instit:	Arm A = **3** Instit 657 ↔ Arm B = **2** Instit 657

+

Overall:	**Arm A = 90**	↔	**Arm B = 95**

d = # Strat = 3

is allocated to arm A (forced)

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Minimization at the EORTC

- **Stratification is an integral part of study design at the EORTC.**
- **Internal SOPs ensure that stratification factors are identified and justified in the early stage of trial design.**
- "… randomization should be stratified for a small number of reliable factors of known prognostic value."
- " … recommended that the randomization procedure is kept simple by limiting the number of stratification factors and to stratify only by the one or two most important prognostic variables in addition to institution."

Future Developments

Threshold

- Default: number of stratification factors
- Can be changed (justification)

Institution

- Default: always included
- Can be excluded (justification)

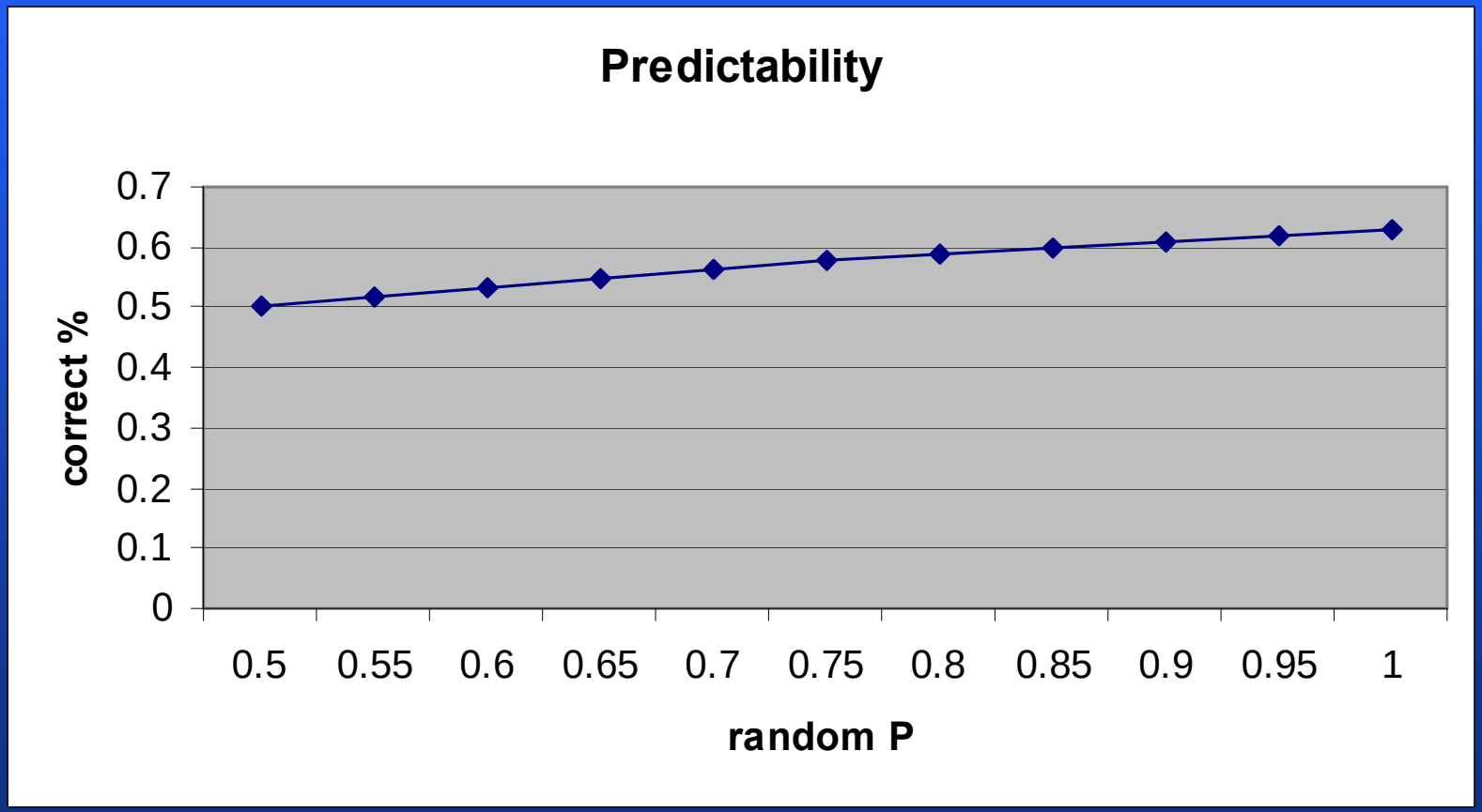
Random Allocation Component

- If threshold exceeded: treatment arm ineligible
- Ineligible arms still possible with low probability

Random Allocation Component

- A random component option is being added in order to prevent completely deterministic allocations.
- Random probability = 0.85-0.90 has only a small impact on the degree of imbalance, both overall and within strata.
- Simulation example: typical Phase III trial
  - 200 patients over 2 arms
  - 30 sites and 2 other binary factors

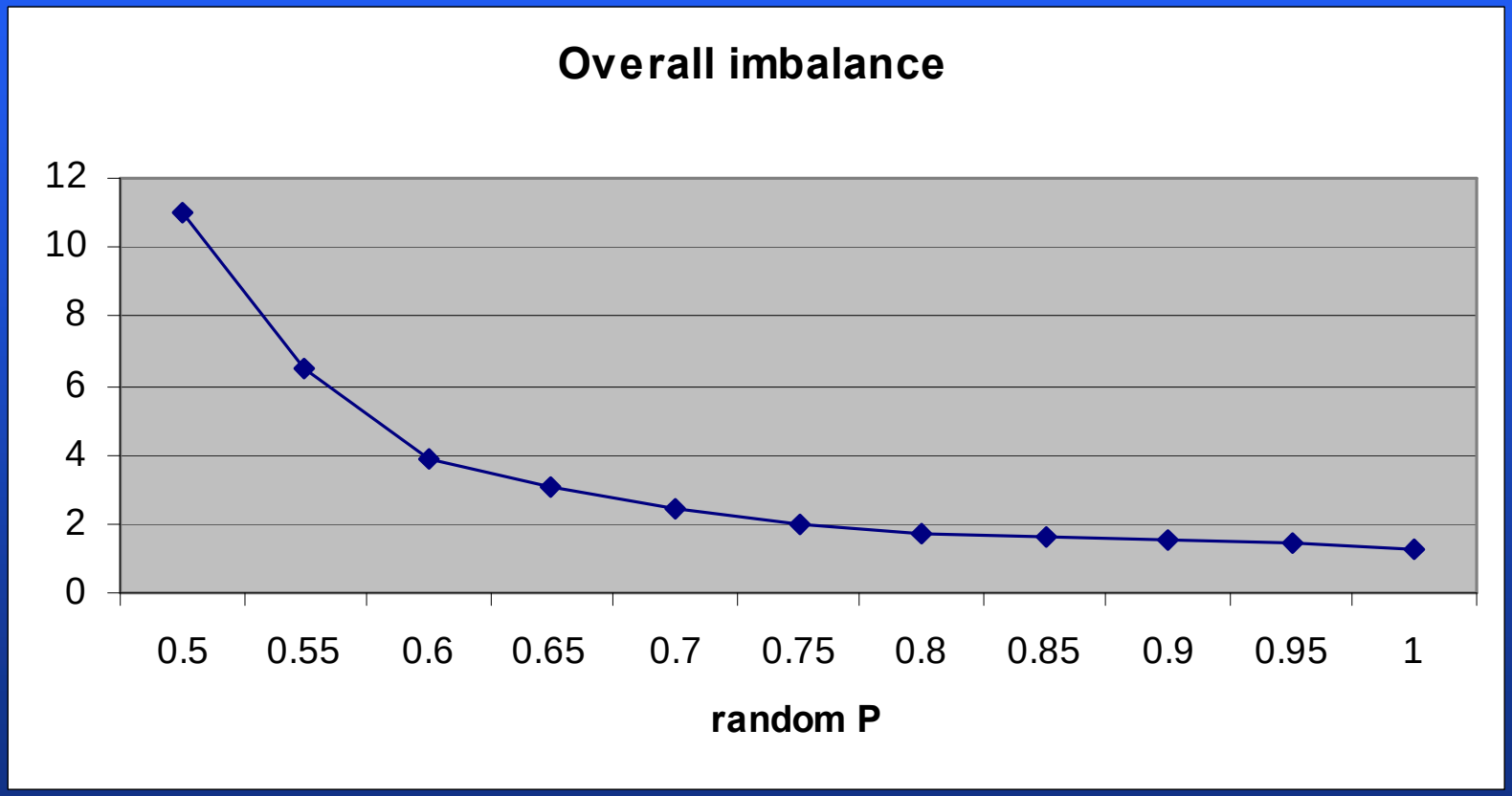
Random Component



Local prediction: within site to the arm with fewest patients

EORTC

Random Component



Imbalance: difference in patients between the two arms

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Other Cooperative Groups

- **NCIC: minimization**
- **MRC: minimization**
- **SGCTG: minimization**
- **SWOG: minimization**
- **AGO: blocks → minimization**
- **NSGO: permuted blocks**
- **RTOG: permuted blocks**
- **ECOG: permuted blocks**
- **…**

→ Huge number of patients.

Regulatory Viewpoints

- **ICH E9: Statistical principles for clinical trials (1998)**
- **"Deterministic dynamic allocation should be avoided and an appropriate element of randomization should be incorporated for each treatment allocation."**

- **CPMP: Points to consider on adjustment for baseline covariates (2003)**
- **"Even if deterministic schemes are avoided, such methods remain highly controversial."**
- **"Dynamic allocation is strongly discouraged."**

EORTC Viewpoints

- **Minimization = safe, reliable, pragmatic**
- **These controversial regulatory guidelines have put unfair pressure on this method.**
- **Adaptation:**
  - **Transparency:** extensive log of each allocation
  - **Flexibility:** extra design parameters
  - **Predictability:** random component

General Issues

- **Predictability**
  - **More of an issue for regulators than for investigators ?**
  - **Deterministic ≠ predictable**
- **Amendments**
  - **Change of stratifications mid-trial**
  - **Technical and practical problems**
- **Faulty randomizations**
  - **Double randomizations, incorrect stratification level**
  - **Not removed/corrected**

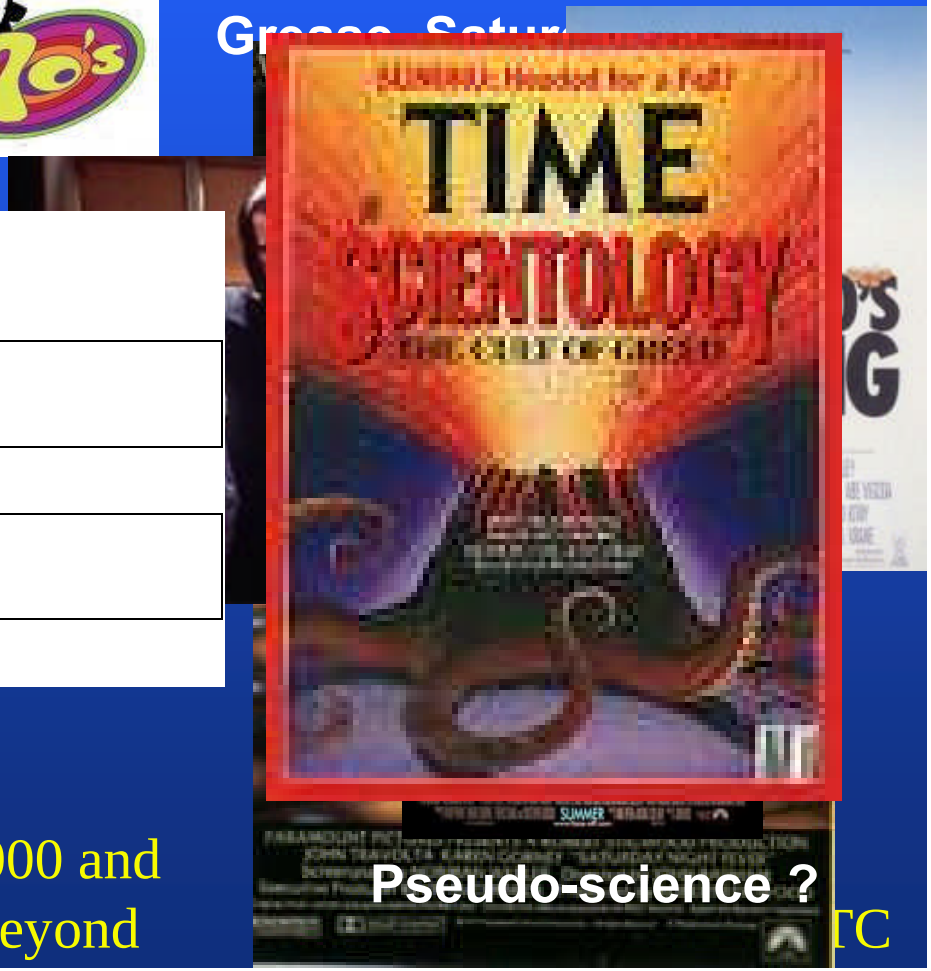
Status of Minimization

Minimization

1975: Pocock & Simon

1976: Freedman & White

John Travolta



Committee for proprietary medicinal products (CPMP)

POINTS TO CONSIDER ON ADJUSTEMENT FOR BASELINE COVARIATES

Pseudo-science ?

2000 and beyond

Pseudo-science ?

TC

Conclusions

- Minimization is a method for which both the EORTC and the clinical trial community at large have extensive experience.
- Minimization can meet the requirements of the EORTC for its trials.
- Recent regulatory guidelines have led to a series of criticisms and counter-criticisms.
- Recent revisions of the EORTC algorithm are a direct consequence of these guidelines.