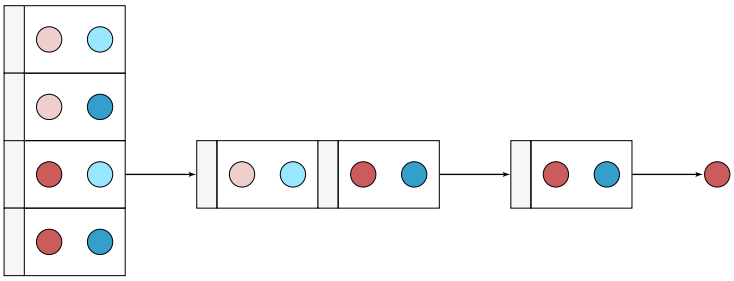
# Patient-oriented Randomisation – a new clinical trial design



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# Danksagung

*„Bernhard von Chartres sagte, wir seien gleichsam Zwerge, die auf den Schultern von Riesen sitzen, um mehr und Entfernteres als diese sehen zu können – freilich nicht dank eigener scharfer Sehkraft oder Körpergröße, sondern weil die Größe der Riesen uns emporhebt.“*

—Johannes von Salisbury: Metalogicon 3,4,46–50—

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# Abstract

In this thesis a new randomisation designs for clinical trials, called patient-oriented randomisation design, is introduced. This design was developed to counter problems of 'classical' randomised controlled trials comparing strategies (consisting of different treatments in each strategy) in presence of heterogeneity in patient-drug-interactions. The discrepancies between daily clinical perception and results of randomised controlled trials lead to the conviction that the methodological approach of 'classical' randomised controlled trials, such as the block randomisation design, is appropriate in this set-up. The patient-oriented approach of the 'CUtLASS' design reflects everyday clinical practice, by allowing for a patient-oriented choice of one treatment of each strategy. The allocation for a strategy is random. However, the results are highly dependent on the physicians' preferences. The goal of the design described here is to take an intermediate path between randomised controlled trials and the 'CUtLASS' design. The idea of the new trial design is to randomise two treatment pairs each consisting of one treatment of the one strategy and one treatment of the other strategy in a first step and subsequently, to involve the investigators in deciding for a pair most appropriate to the patients' needs and then to randomise the allocation to one treatment of that chosen pair.

After a short introduction, in Chapter 2 basic definitions and notations are given. The considerations concentrate on the properties of the patient-oriented randomisation design which depend mainly on the number of treatments of each strategy. An advantage of the patient-oriented randomisation design (compared to classical randomisation designs) is that in some cases a clear patient-oriented treatment decision of the physician can be seen and investigated.

The patient-oriented decision in the 'CUtLASS' and the patient-oriented randomisation design can lead to unbalanced treatment sample size in each strategy. Chapter 3 investigates the changes of the allocation probability of each treatment and determines the minimum and the maximum allocation probability in both designs. The investigation shows that the interval of possible values of allocation probabilities is lager in the 'CUtLASS' design. However, the patient-oriented randomisation design ensures that each treatment is in fact administered in the study. Hence, it is possible to compute the number of patients needed to avoid poorly represented treatments and poorly powered comparisons.

After this, the practical implementation of the patient-oriented randomisation design are looked at and methods to estimate the probability of imbalance are presented. The block length of the patient-oriented randomisation design is large, hence, modification for the creation for the random list are possible and effective to reduce the probability of imbalance.

Finally, Chapter 5 deals with a statistical model to compare two strategies consisting of different treatments. Basic definitions and notations are given for unbalanced one-way classification with fixed effects and the concept of contrasts. Additionally, the required sample size calculation is presented. The power of the associated contrast test depends

particularly on the allocation of sample size in each treatment and the expected effect between both strategies. The final consideration shows that heterogeneity of patient-drug-interaction lead to no effect in the 'Block' design. Randomisation designs such as the 'CUtLASS' design and the patient-oriented randomisation design only work as well as the physicians selecting the treatments. In a patient-oriented randomisation design, it can be distinguished between patients receiving the treatment not only due to randomisation but due to a patient-oriented decision of the physician (patient-oriented treated patients) and patients receiving the treatment due to randomisation's reasons (randomised choice treated patients). Therefore, the patient-oriented randomisation design allows to test the difference in treatment means between patient-oriented treated patients and randomised choice treated patients in each treatment, each strategy, or overall. In particular, the possibility to analyse the difference between strategies for subgroups consisting of only randomised choice treated patients or only patient-oriented choice treated patients help to test the assumptions about the heterogeneity of patient-drug-interaction in the patient-oriented randomisation design. In the 'CUtLASS' design, it is not possible to answer this important question.

The conclusion consists of a discussion of the results as well as important findings. An outlook on possible future work is also presented.

# Zusammenfassung

In dieser Arbeit wird ein neues Randomisierungsverfahren für klinische Studien eingeführt, die patienten-orientierte Randomisierung bzw. im englischen „patient-oriented randomisation design“. Dieses Verfahren wurde entwickelt, um dem Problem von klassischen randomisierten, kontrollierten klinischen Studien entgegen zu wirken, die bei heterogener Patienten-Behandlungs-Wechselwirkung auftritt, wenn Strategien bestehend aus vielen Therapiemöglichkeiten verglichen werden. Die Diskrepanz zwischen der täglichen klinischen Wahrnehmung und den Ergebnissen von randomisierten und kontrollierten klinischen Studien führt zu der Überzeugung, dass der methodische Ansatz der klassischen Randomisierungverfahren, wie der Blockrandomisierung, nicht das geeignete Mittel für die Untersuchung dieser Fragestellung ist. Es gibt bereits patienten-orientierte Ansätze, wie das „CUtLASS“-Verfahren, um die tägliche klinische Praxis wiederzuspiegeln. Hierbei kann der Arzt innerhalb jeder Strategie eine Behandlung wählen und die Strategie, die der Patient bekommen soll, wird anschließend randomisiert. Jedoch hängen bei diesem Verfahren die Resultate stark von der Arztentscheidung ab. Das Ziel des hier vorgestellten Randomisierungsverfahrens ist ein Mittelweg zwischen dem Wunsch nach Randomisierung wie in den randomisierten kontrollierten Studien und der ärztlichen Entscheidung wie im „CUtLASS“-Design zu nehmen. Die Idee des neuen Randomisierungsverfahrens ist zwei Behandlungspaare jeweils bestehtend aus einer Behandlung aus jeder Strategie im ersten Schritt zu randomisieren. Anschließend entscheidet der Arzt, welches Paar zur Behandlung des Patienten aufgrund seiner Krankengeschichte besser geeignet ist. Im zweiten Schritt wird der Patient zu einer der zwei Behandlungen des gewählten Paars und damit zu einer der beiden Strategien randomisiert.

Nach der Einleitung, werden in Kapitel 2 die wesentlichen Definitionen und Notationen gegeben, um im Weiteren die Eigenschaften des patienten-orientierten Randomisierungsverfahrens zu untersuchen. Die Eigenschaften hängen hauptsächlich von der Anzahl der Behandlungen in beiden Strategien ab, daher sollte deren Festlegung bei der Studienplanung wohlüberlegt sein. Ein Vorteil der patienten-orientierten Randomisierung gegenüber den klassischen Randomisierungsverfahren ist, das in einigen Fällen eine klare patienten-orientierte Entscheidung des Arztes zwischen zwei Behandlungen einer Strategie beobachtet und untersucht werden kann.

Die patienten-orientierte Entscheidung im „CUtLASS“-Verfahren und im patienten-orientierten Randomisierungsverfahren führt zu unbalancierten Behandlungsfallzahlen in jeder Strategie. In Kapitel 3 werden die Veränderungen in der Allokationswahrscheinlichkeit der einzelnen Behandlungen untersucht und die minimale und die maximale Allokationswahrscheinlichkeit in beiden Verfahren bestimmt. Die Untersuchungen zeigen, dass die Spannweite der möglichen Allokationswahrscheinlichkeiten im „CUtLASS“-Verfahren breiter ist als im patienten-orientierten Randomisierungsverfahren. Dahingegen sichert das patienten-orientierte Randomisierungsverfahren ab, dass jede Behandlung auch tatsächlich mit einem gewissen Prozentsatz in der Studie angewendet wird. Damit ist man

bei der Planung der Studie in der Lage, die Fallzahl zu berechnen, um unterpresentierte Behandlungen und unterpowerte Vergleiche zu vermeiden.

Schließlich wird in Kapitel 5 ein statistisches Model vorgestellt, um zwei Strategien zu vergleichen. Wesentliche Definitionen und Notationen werden zur unbalancierten Einfachklassifikation und dem Konzept der Kontraste gegeben. Außerdem wird die erforderliche Fallzahlplanung vorgestellt. Die Power des zugehörigen Kontrasttests hängt unter anderem von der Größe der Behandlungsfallzahlen und dem erwarteten Effekt zwischen den Strategien ab. Die abschließenden Betrachtungen zeigen, dass die Heterogenität in der Patienten-Behandlungs-Wechselwirkung dazu führen kann, das kein Effekt in der Blockrandomisierung zu beobachten ist. Die Untersuchungen zeigen aber auch, dass die patienten-orientierten Verfahren, wie das „CUtLASS"-Verfahren oder das patienten-orientierte Randomisierungsverfahren nur so gut sind, wie die Qualität der patienten-orientierten Wahl es zulassen. Zusätzlich kann im patienten-orientierten Randomisierungsverfahren zwischen Patienten unterschieden werden, die die Behandlung nur aufgrund des Randomisierungsprozesses erhalten (randomisiert behandelte Patienten) und jenen, die die Behandlung neben dem Randomisierungsprozesses auch aufgrund der Arztwahl erhalten haben (patienten-orientiert behandelte Patienten). Daher erlaubt das patienten-orientierte Randomisierungsverfahren den Unterschied zwischen randomisiert behandelten Patienten und patienten-orientiert behandelten Patienten in jeder Behandlung, in jeder Strategie und in insgesamt zu testen. Insbesondere ist es möglich die Unterschiede zwischen den Strategien innerhalb von Subgruppen bestehend aus randomisiert behandelten Patienten oder patienten-orientiert behandelten Patienten zu analysieren. Damit können die Annahmen über die heterogene Patienten-Behandlungs-Wechselwirkung im patienten-orientierten Randomisierungverfahren überprüft werden. Im „CUtLASS"-Verfahren ist es nicht möglich, diese wichtige Frage zu klären.

Die Arbeit schließt mit einer Disskussion über die Resulte und einem Ausblick auf mögliche weiterführende Forschungsthemen ab.

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## Abbreviations

| Abbreviation | Explanation |
|---|---|
| AP | Allocation probability |
| BMBF | German Federal Ministry of Education and Research |
| CATIE | Clinical Antipsychotic Trial of Intervention Effectiveness |
| cf. | Confer, meaning 'compare' |
| const. | Constant |
| CUtLASS | Cost Utility of the Latest Antipsychotic drugs in Schizophrenia Study |
| e.g. | Exempli gratia, meaning 'for example' |
| EUFEST | European First Episode Schizophrenia Trial |
| i.i.d. | independent and identically distributed |
| i.e. | Id est, meaning 'that is to say' |
| NeSSy | Neuroleptic Strategy Study |
| POR | Patient-oriented randomisation |
| RCT | Randomised, controlled trial |
| TPC | Two-pair combination |

## Symbols

| Symbol | Explanation |
|---|---|
| Study designs | |
| $\text{POR}_{k,l}$ | Patient-oriented randomisation design for two strategies with $k$ and $l$ treatments |
| $\text{POR}_{2,3}$ | NeSSy design |
| $\text{Block}_{k,l}$ | Balanced block randomisation design for two strategies with $k$ and $l$ treatments |
| $\text{CUtLASS}_{k,l}$ | CUtLASS design for two strategies strategies with $k$ and $l$ treatments |

| Symbol | Explanation |
|---|---|
| **Sets** | |
| $\mathcal{A}$, $\mathcal{B}$ | Strategy groups which should be compared |
| $\mathcal{A} \times \mathcal{B}$ | Cartesian Product between the two sets $\mathcal{A}$ and $\mathcal{B}$ |
| $\mathcal{A}^R$ | Set of treatments of strategy $\mathcal{A}$ allocated to patients due to patient-oriented decisions of the physicians |
| $\mathcal{A}^P$ | Set of treatments of strategy $\mathcal{A}$ allocated to patients due to randomisation's reasons |
| $\mathcal{B}^R$ | Set of treatments of strategy $\mathcal{B}$ allocated to patients due to patient-oriented decisions of the physicians |
| $\mathcal{B}^P$ | Set of treatments of strategy $\mathcal{B}$ allocated to patients due to randomisation's reasons |
| $P_1$, $P_2$ | Heterogeneous populations types of patients |
| $\mathcal{P}$ | Power set |
| $\mathcal{TPC}_{k,l}$ | Set of all two-pair combinations from two strategies with $k$ and $l$ treatments |
| $[A_i,A_{i'}]$ | Equivalence class of unordered $\mathcal{A}$-pairs; for $i = i'$ calling it an identical $\mathcal{A}$-pair otherwise a mixed $\mathcal{A}$-pair |
| $\mathcal{A}^{\otimes}_{k,l}\mathcal{A}$ | Set of all unordered equivalence classes of $\mathcal{A}$-pairs |
| $[B_j,B_{j'}]$ | Equivalence class of unordered $\mathcal{B}$-pairs; for $j = j'$ calling it an identical $\mathcal{B}$-pair otherwise a mixed $\mathcal{B}$-pair |
| $\mathcal{B}^{\otimes}_{k,l}\mathcal{B}$ | Set of all unordered equivalence classes of $\mathcal{B}$-pairs |
| $\mathrm{POD}_{k,l}$ | Set of all informative combinations respectively the set of all two-pair combinations with clear patient-oriented decisions |
| $\mathbb{N}$ | Set of the natural numbers, i.e. positive integers |
| $\mathbb{R}$ | Set of the real numbers |
| **Elements** | |
| $A_1, \ldots, A_k$ | Treatments in strategy $\mathcal{A}$ |
| $B_1, \ldots, B_l$ | Treatments in strategy $\mathcal{B}$ |
| $A_i$ | One treatment of strategy $\mathcal{A}$ |
| $A_i^R$ | Treatment $i$ of strategy $\mathcal{A}$ allocated to patients due to randomisation's reasons |
| $A_i^P$ | Treatment $i$ of strategy $\mathcal{A}$ allocated to patients due to a patient-oriented decision of the physician |
| $B_j$ | One treatment of strategy $\mathcal{B}$ |
| $B_j^R$ | Treatment $j$ of strategy $\mathcal{B}$ allocated to patients due to randomisation's reasons |
| $B_j^P$ | Treatment $j$ of strategy $\mathcal{B}$ allocated to patients due to a patient-oriented decision of the physician |
| $(A_i,B_j)$ | Pair consisting of one treatment $A_i \in \mathcal{A}$ and one treatment $B_j \in \mathcal{B}$ |
| $[(A_i, B_j),(A_{i'}, B_{j'})]$ | Two-pair combination |
| $\omega_1, \ldots, \omega_{\lvert\mathcal{A}\times\mathcal{B}\rvert}$ | Elements of $\mathcal{A} \times \mathcal{B}$ |

| Symbol | Explanation |
|---|---|
| **Elements** | |
| $\omega_n$ | One element of $\mathcal{A} \times \mathcal{B}$ |
| $\text{TPC}_1, \ldots, \text{TPC}_{\lvert\mathcal{TPC}_{k,l}\rvert}$ | Elements of $\mathcal{TPC}_{k,l}$ |
| $\text{TPC}_m$ | One element of $\mathcal{TPC}_{k,l}$ |
| $(\text{TPC}_m, \mathcal{A})$, $(\text{TPC}_m, \mathcal{B})$ | Tuples of the randomisation list of a $\text{POR}_{k,l}$ design |
| **Sequences** | |
| $(a_{k,l})_{k\in\mathbb{N},l\in\mathbb{N}\setminus\{1\}}$ | Sequence in $k$ and $l$ |
| $(a_{k,.})_{k\in\mathbb{N}\setminus\{1\}}$ | Sequence with $l = const.$ |
| $(a_{.,l})_{l\in\mathbb{N}\setminus\{1\}}$ | Sequence with $k = const.$ |
| **Numbers** | |
| $k$ | Number of treatments in strategy $\mathcal{A}$ |
| $l$ | Number of treatments in strategy $\mathcal{B}$ |
| $h$ | Predefined block length |
| $\text{H}_{k,l}^{\text{Block}}$ | Minimum block length of a $\text{Block}_{k,l}$ design |
| $\text{LCM}_{k,l}$ | Least common multiple of $k$ and $l$ |
| $\text{H}_{k,l}^{\text{POR}}$ | Minimum block length of a $\text{POR}_{k,l}$ design |
| $\lvert\ldots\rvert$ | Number of elements in the set between the draw stokes |
| $N$ | Total sample size |
| $N_{\mathcal{A}}$ | Sample size of patients assigned to strategy $\mathcal{A}$ |
| $N_{\mathcal{B}}$ | Sample size of patients assigned to strategy $\mathcal{B}$ |
| $K$ | Number of strata (centres) |
| $\tau$ | Number of two-pair combinations |
| $T$ | Number of blocks |
| $t$ | Number of filled blocks |
| $h_j$ | Sub block length |
| $J$ | Number of sub blocks with sub block length $h_j$ in the minimum block with minimum block lenght $\text{H}_{k,l}^{\text{POR}}$ |
| $n_j$ | Number of patients treated with treatment $j$ |
| $n$ | Number of patients treated with treatment $j$ for balanced groups |
| **Distributions and quantiles** | |
| $H(h,h/2,r)$ | Hypergeometric distribution with $h$, $h/2$ and $r$ |
| $H(h,2,\ldots,2,r)$ | Multivariate hypergeometric distribution with $h$, $(2,\ldots,2)$ and $r$ |
| $\mathcal{N}(\theta,\sigma^2)$ | Normal distribution with mean $\theta$ and variance $\sigma^2$ |
| $\Phi(.)$ | Distribution function of the standard normal distribution |
| $B(h,p)$ | Binomial distribution with $h$ and probability $p$ |
| $F$ | Test statistic of the omnibus null hypothesis |

| Symbol | Explanation |
|---|---|
| **Distributions and quantiles** | |
| $F_\psi$ | Test statistic of the associated null hypotheses $H_\psi$ |
| $F_{1-\alpha}(\mathrm{df_{BG}},\mathrm{df_{RES}})$ | $(1-\alpha)$-quantile of the $F$- distribution with $\mathrm{df_{BG}}$ and $\mathrm{df_{RES}}$ degrees of freedom |
| $t_\psi$ | Test statistic of the associated null hypotheses $H_\psi$ |
| $t(\mathrm{df_{RES}},\delta)$ | Noncentral $t$-distribution with $\mathrm{df_{RES}}$ degrees of freedom and noncentrality parameter $\delta$ |
| $t_{1-\alpha}(\mathrm{df_{RES}})$ | $(1-\alpha)$-quantile of the Student's central $t$-distribution with $\mathrm{df_{RES}}$ degrees of freedom |
| $t_{1-\alpha}(\mathrm{df_{RES}},\delta)$ | $(1-\alpha)$-quantile of the Student's $t$-distribution noncentral with $\mathrm{df_{RES}}$ degrees of freedom and noncentrality parameter $\delta$ |
| **Random variables and realisations** | |
| $\Gamma$ | Random variable describing the randomisation in two-pair combinations (first step of randomisation in a patient-oriented design) |
| $\Theta$ | Random variable describing the distribution of the patient-oriented step of randomisation in a $\mathrm{POR}_{k,l}$ design |
| $\Theta_C$ | Special case of $\Theta$ describing the selection of random pairs containing $C$ when ever possible |
| $\Theta_{\bar{C}}$ | Special case of $\Theta$ describing the deselection of random pairs containing $C$ when ever possible |
| $\Theta^{\mathrm{CUtLASS}}$ | Random variable describing the distribution of the patient-oriented step in a $\mathrm{CUtLASS}_{k,l}$ design |
| $\Theta_C^{\mathrm{CUtLASS}}$ | Special case of $\Theta^{\mathrm{CUtLASS}}$ describing the selection of treatment $C$ |
| $\Theta_{\bar{C}}^{\mathrm{CUtLASS}}$ | Special case of $\Theta^{\mathrm{CUtLASS}}$ describing the deselection of treatment $C$ |
| $\Psi$ | Random variable describing the randomisation in strategy (second step of randomisation in a patient-oriented design) |
| $\Psi_{\mathcal{A}}$ | Random variable describing the randomisation in two-pair combination and in strategy $\mathcal{A}$ |
| $\Psi_{\mathcal{B}}$ | Random variable describing the randomisation in two-pair combination and in strategy $\mathcal{B}$ |
| $\Upsilon$ | Random variable describing the randomisation in a $\mathrm{Block}_{k,l}$ design |
| $R$ | Number of assignments issued in the last block |
| $r$ | Observed number of assignments issued in the last block |
| $R_i$ | Number of assignments issued in the last block of the $i$th stratum |

| Symbol | Explanation |
|---|---|
| Random variables and realisations | |
| $r_i$ | Observed number of assignments issued in the last block of the $i$th stratum |
| $S$ | Number of assignments to strategy $\mathcal{A}$ issued in the last block |
| $s$ | Observed number of assignments to strategy $\mathcal{A}$ issued in the last block |
| $S_i$ | Number of assignments to strategy $\mathcal{A}$ issued in the last block of the $i$th stratum |
| $s_i$ | Observed number of assignments to strategy $\mathcal{A}$ issued in the last block of the $i$th stratum |
| $D$ | Random variable describing the total imbalance between the strategies in the last block |
| AD | Random variable describing the absolute value of the total imbalance in the last block |
| $D_i$ | Random variable describing the imbalance between strategies in the last block of the $i$th stratum |
| $X_m$ | Random variable describing the number of occurrences of the $m$th two-pair combination |
| $\vec{X} = (X_1, \ldots, X_\tau)$ | Vector of random variables $X_1, \ldots, X_\tau$ |
| $X_m^{t+1}$ | Random variable describing the number of occurrences of $m$th two-pair combination in the $(t+1)$th block |
| $X_m^{\text{tot}}$ | Random variable describing the number of occurrences of $m$th two-pair combination |
| $X_{mi}$ | Random variable describing the number of assignments to $m$th two-pair combination in the last block of the $i$th stratum |
| $x_{mi}$ | Observed number of assignments to $m$th two-pair combination in the last block of the $i$t stratum |
| $\vec{X}_m = (X_{m1}, \ldots, X_{mK})$ | Vector of random variables describing the number of assignments to the $m$the two-pair combinations in all strata |
| $Y$ | Responds variable in the one-way classification, normally distributed |
| $Y_{ji}$ | Responds for subject $i$ int treatment level $j$ |
| $\varepsilon_{ji}$ | Error associated with $Y_{ji}$ |
| $y_{ji}$ | Realisation of the random variable $Y_{ji}$ |
| Probabilities | |
| $p_\Theta^m$ | Probability of the physician's decision for random pair 1 by two-pair combination $m$ |
| $q_\Theta^m$ | Probability of the physician's decision for random pair 2 by two-pair combination $m$ |

| Symbol | Explanation |
|---|---|
| **Probabilities** | |
| $p_\Psi$ | Probability for a patient receiving a treatment of strategy $\mathcal{A}$ |
| $p_\Psi$ | Probability for a patient receiving a treatment of strategy $\mathcal{A}$ |
| $q_\Psi$ | Probability for a patient receiving a treatment of strategy $\mathcal{B}$ |
| $p_\mathcal{A}$ | Probability for two-pair combinations with one identical $\mathcal{A}$-pair in the set of two-pair combinations |
| $q_\mathcal{A}$ | Probability for two-pair combinations with one mixed $\mathcal{A}$-pair in the set of two-pair combinations |
| $p_\mathcal{B}$ | Probability for two-pair combinations with one identical $\mathcal{B}$-pair in the set of two-pair combinations |
| $q_\mathcal{B}$ | Probability for two-pair combinations with one mixed $\mathcal{B}$-pair in the set of two-pair combinations |
| $p_\Theta^{ij}$ | Probability of the physician's decision for the treatment pair $(A_i, B_j)$ |
| $P_i$ | Probability of a patient belonging to the $i$th stratum |
| $p$ | Probability of assignments issued in the last block |
| $p_i$ | Probability of assignments issued in the last block of the $i$th stratum |
| **Parameters of the statistical analysis** | |
| $\mu_j$ | Treatment group mean of treatment $j$ |
| $\sigma_\varepsilon^2$ | Error variance |
| $\sigma_\mu^2$ | Parameter indicating the extent to which the treatment effect differs between the groups |
| $\mu$ | Expected value of the overall population |
| $\tau_j$ | Treatment effect of $j$th treatment |
| $\hat{\mu}$ | Estimation of the expected value of the overall population |
| $\bar{y}_{..}$ | Grand mean |
| $\hat{\mu}_j$ | Estimation of the expected value of treatment $j$ |
| $\hat{\mu}_j - \hat{\mu}$ | Estimation of the treatment effect of treatment $j$ |
| $\hat{\mu}_\mathcal{A}$ | Estimation of the mean response in strategy $\mathcal{A}$ |
| $\hat{\mu}_\mathcal{B}$ | Estimation of the mean response in strategy $\mathcal{B}$ |
| $e_{ji}$ | Residual effect |
| $\psi$ | Linear contrast among treatment group means |
| $\psi_0$ | Strategy comparison contrast |
| $c_i$ | Coefficients of the linear contrast |
| $\hat{\psi}$ | Least-squares estimator of $\psi$ |
| $\sigma_{\hat{\psi}}^2$ | Variance of $\hat{\psi}$ |
| $\hat{\sigma}_{\hat{\psi}}^2$ | Variance estimator of $\hat{\psi}$ |
| $\bar{y}_{j.}$ | Mean in the treatment level $j$ |
| $\mathrm{SS}_\mathrm{TOT}$ | Total sum of squares |
| $\mathrm{SS}_\mathrm{BG}$ | Sum of squares between groups |
| $\mathrm{SS}_\mathrm{RES}$ | Sum of squares within groups |

| Symbol | Explanation |
|---|---|
| Parameters of the statistical analysis | |
| $\mathrm{SS}_{\psi}$ | Sum of squares for a contrast $\psi$ |
| $\mathrm{MS}_{\mathrm{TOT}}$ | Mean total squares |
| $\mathrm{MS}_{\mathrm{BG}}$ | Mean squares within groups |
| $\mathrm{MS}_{\mathrm{RES}}$ | Mean squares between groups |
| $\mathrm{MS}_{\psi}$ | Mean squares for a contrast $\psi$ |
| df | Degrees of freedom |
| $\mathrm{df}_{\mathrm{TOT}}$ | Degrees of freedom associated with $\mathrm{SS}_{\mathrm{TOT}}$ |
| $\mathrm{df}_{\mathrm{BG}}$ | Degrees of freedom associated with $\mathrm{SS}_{\mathrm{BG}}$ |
| $\mathrm{df}_{\mathrm{RES}}$ | Degrees of freedom associated with $\mathrm{SS}_{\mathrm{RES}}$ |
| $\rho_{12}$ | Correlation between two contrasts $\psi_1$ and $\psi_2$ |
| $H$ | Null hypotheses |
| $H_{\psi}$ | Null hypotheses associated with contrast $\psi$ |
| $K$ | Alternative hypotheses |
| $K_{\psi}$ | Alternative hypotheses associated with contrast $\psi$ |
| $\mathcal{H}$ | Global null hypotheses |
| $\Delta$ | Expected effect between both strategies |
| $\delta$ | Noncentrality parameter of the $t$-distribution |
| $\eta$ | Factor of the noncentraility parameter $\delta$ depending on the coefficients of the contrast and the treatment's sample sizes |
| $\kappa$ | Probability of a patient entering the study to be in population $P_1$ |
| $\rho$ | Probability that a physician chooses the most suitable random pair (from a two-pair combination in a $\mathrm{POR}_{k,l}$ design) for a given patient |
| $\nabla$ | Relative effect of the strategy mean differences |
| $\nabla_{\mathrm{SCC}}$ | Relative effect of the strategy comparison contrast |
| Operators | |
| $\mathbb{P}$ | Probability measure |
| $\mathbb{P}_{\Gamma}$ | Law of $\Gamma$ under $\mathbb{P}$ |
| $\mathbb{E}[X]$ | Expectation of random variable $X$ |
| $\mathbb{E}[X\|R]$ | Conditional expectation of $X$ given $R$ |
| $\mathrm{Var}[X]$ | Variance of random variable $X$ |
| $\mathrm{Var}[X\|R]$ | Conditional variance of $X$ given $R$ |
| $\times$ | Cartesian product |
| $\overset{\times}{_{k,l}}$ | Unordered cartesian product of equal sets without the set of pairs with equal elements |
| $\overset{\otimes}{_{k,l}}$ | Equivalence class of unordered cartesian product of two sets |
| $S^2(\vec{X})$ | Variance estimator of $X_i$, where $\vec{X} = (X_1, \ldots, X_\tau)$ vector of identically and independently distributed random variables $X_i$ |

| Symbol | Explanation |
|---|---|
| **Operators** | |
| $\asymp$ | 'Equally preferred' relation between two treatments of on strategy |
| $\succeq$ | 'Preferred to' relation between two treatments of on strategy |
| **Other** | |
| $\overset{A}{\sim}$ | Approximative distributed |
| $\overset{\text{i.i.d.}}{\sim}$ | Independent and identically distributed |
| $C_1$, $C_2$, $C_3$ | Abbreviations for centre 1, centre 2 and centre 3 |

CHAPTER 1

# Introduction

## 1.1 Introduction

'The "gold standard" for clinical studies is a randomised controlled trial (RCT) usually comparing specific treatments, for example a new drug, a comparator drug or placebo. This comparison is especially appropriate when efficacy and safety of new drugs are being investigated. The procedure becomes more complicated if the scientific problem expands to strategy comparison, in which each strategy includes various treatments.'(Schulz et al., 2016a) Firstly, we describe in the following section the background and problems involving strategy comparison in the psychiatric research field to motivate the development of a new clincial trial design. Some parts of this section have already been introduced in the publications Schulz et al. (2016a) and Schulz et al. (2016b) which contain an example of the below presented trial design. These contents are marked accordingly. Afterwards, we have a general look at the problems and the consequences if we use other trial designs. In the last section of this chapter, we introduce the idea of a new clinical trail design to solve the problems and describe the goal of this thesis.

## 1.2 Motivation and background

'The starting point for the development of this design is a debate in the psychiatric community. Based on everyday practice it is widely accepted that second-generation antipsychotics [...] are considered to be the treatment of choice in the therapy of schizophrenic disorders (Gaebel et al., 2006, p. 82). However, the general superiority of [second-generation antipsychotics] over the first-generation antipsychotics [...] could not be clearly demonstrated in recent controlled clinical trials such as the European First Episode Schizophrenia Trial (EUFEST), Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) and Cost Utility of the Latest Antipsychotic drugs in Schizophrenia Study (CUtLASS)(Kahn et al., 2008; Lieberman et al., 2005; Jones et al., 2006).'(Schulz et al., 2016a) The questions why do the clinical trials show results contradicting practical experience and are either the practical experiences or the results of clinical trials wrongly interpreted immediately arose. No definite fault has been found with either. The methodological problems of those trials have been discussed by Naber and Lambert (2009) and Constantine and Tandon (2007). As background, we consider the advantages and disadvantages for a strategy decision (to use second-generation or first-generation antipsychotics) to see the problems of the suitability of the methological approach.

'EUFEST is an open, randomised trial [comparing the effectiveness of haloperidol to second-generation antipsychotics] in first-episode schizophrenia. CATIE Phase 1 is a double-blind trial comparing perphenazine with four [second-generation antipsychotics]. One disadvantage of both studies is that only one representative was chosen in the group of [first-generation antipsychotics] to compare both strategies. The overall CATIE study design is more complex and allowed for patients who had discontinued one antipsychotic study drug to enter subsequent phases (2 and later 3) of the study and receive another antipsychotic study drug (Lieberman et al., 2005). Thus, the CATIE study is a representative of the Sequential Multiple Assignment Randomised Trials (Dawson and Lavori, 2012; Lavori et al., 2000; Murphy, 2005), whose primary goal is to yield information for the development of adaptive intervention strategies. A further goal is to collect information on candidate tailoring variables (Lei et al., 2012). This differs slightly from the goal of comparing two one-step strategies (whether to use [first-generation] or to use [second-generation antipsychotics]). Thus, the CATIE study provided no clear answer to the question of strategy comparison. It does, however, "provide more evidence to clinicians, patients, and policy makers that response to antipsychotic drug treatment is heterogeneous. The individual variations in response to medications are likely due to multiple factors that may be difficult to elucidate" (Stroup et al., 2007). [The problem is more complex than a simple randomised strategy comparison.] This difficulty underlines an additional condition important for [the new] design: the treatments even in one strategy perform differently for different patients, but subgroups which might account for these differences are not identifiable. This implies that in a design with simple block randomisation, such as EUFEST and CATIE Phase 1, the results from the responders and non-responders may cancel each other out.

To measure the actual strategy effect [in practice], the physician should be involved in the decision concerning trial treatment within each strategy, taking risks and healing opportunities of different drugs for each patient into account. This means using a design close to everyday practice. Despite these points of criticism, however, we must not return to mere observational studies, because, in fact, randomisation is the only way that effectively deals with the risk of bias by selection and confounding (Kleijnen et al., 1997). The challenge is to combine the advantages of an RCT approach with the advantage of taking the physicians' expertise appropriately into account. [A] patient-oriented, straightforward RCT design for comparing two strategies in heterogeneous patient collectives was implemented in the CUtLASS study (Jones et al., 2006).

The CUtLASS study is an open-label trial, in which each psychiatrist chooses one of 13 [first-generation antipsychotics] and one of four [second-generation antipsychotics] before randomisation to one of these drugs. This patient-oriented approach for treatment selection and without blinding is very close to everyday practice. However, the fact that the physician can freely choose from a large number of medications can lead to several problems partly visible in the CUtLASS study. For an ideal situation, every physician should be as thoroughly knowledgeable and experienced as possible with all 17 drugs to be able to decide objectively on the best treatment in each strategy. In practice however, the physicians' preferences are often based on previous positive experience with a certain drug or on information gathered from courses, literature or advertising. Thus the physician may miss the most effective drug of a strategy collection because he has never used it or has received misleading information (see also Korn and Baumrind (1998)). This selection bias will influence the study.

A related problem is the distribution of patients to the drugs tested, especially for the [first-generation antipsychotics]. Half of the patients in the [first-generation antipsychotic]

group received just one drug and only zero to three patients received any of the other nine out of 13 drugs. The question arises why aren't the physicians using the full range of drugs available. Theoretically, the drugs within both strategies should reflect the real market distribution. This is obviously not the case. In the worst case scenario of the CUtLASS design, however, only one treatment in one strategy may be selected, resulting in a one-to-many drug comparison such as in EUFEST and CATIE, and not in a real comparison of strategies with patient-oriented treatment. Thus, the physicians' preferences may lead to poorly represented and thus underpowered comparisons, especially for new drugs or drugs with changed dosage or indications. With studies of the CUtLASS design, the study yields no evidence for drugs provided in the study design but not used. Furthermore, blinding is an issue. In the CUtLASS study the physicians [knew] if they had given a drug not belonging to their favoured strategy. This occurred in about 50% of cases.

In conclusion, the CUtLASS design already took a great step towards a more patient-oriented approach to testing, while EUFEST and CATIE continue to represent the "classical" RCT approach, ensuring systematic comparisons independent of the physician's preference.' Schulz et al. (2016a)

## 1.3 Problem

The previous section describes the motivation and background of the development of the new clinical trial design in context of the debate in the psychiatric community. However, we will concentrate on the core of our issue and asking what happens to strategy comparison in presence of heterogeneity, if not all patients respond to the same drug equally well. Let us consider a hypothetical clinical trial in which we compare two different strategies $\mathcal{A}$ and $\mathcal{B}$. Each strategy consists of two different treatments $A_1, A_2 \in \mathcal{A}$ and $B_1, B_2 \in \mathcal{B}$. We also suppose that we have two different population types $P_1$ and $P_2$ whose response behaviour is given by Table 1.1.

| Strategy | Treatment | Response rate by population | |
|---|---|---|---|
| | | $P_1$ | $P_2$ |
| $\mathcal{A}$ | $A_1$ | 60% | 20% |
| | $A_2$ | 20% | 60% |
| $\mathcal{B}$ | $B_1$ | 40% | 40% |
| | $B_2$ | 40% | 40% |

Table 1.1: Hypothetical response behaviour of two different populations $P_1$ and $P_2$ with two strategies $\mathcal{A}$ (with treatments $A_1$ and $A_2$) and $\mathcal{B}$ (with treatments $B_1$ and $B_2$).

In practice, we don not know how many population types we have and how the treatments perform in the different population types. In our example, the treatments of strategy $\mathcal{A}$ work differently in different populations. For the first hypothetical implementation to investigate the question of strategy comparison, we use a randomised trial with a block randomisation as used in EUFEST or CATIE. The block length should be a multiple of four and we assume that all treatments in all populations are balanced. The patients treated with treatment $A_1$ from strategy $\mathcal{A}$ have an average response rate of 40% and also the

patients treated with treatment $A_2$ have an average response rate of 40%. In total strategy $\mathcal{A}$ has an average response rate of 40%. In the same way, we get an average response rate of 40% for patients treated with treatments of strategy $\mathcal{B}$. Finally, there are no differences between both strategies, even though in both populations, there is a treatment in $\mathcal{A}$ which is superior to all treatments from $\mathcal{B}$. Therefore, under an ideal patient- or population-oriented treatment allocation (disregarding randomisation), one would expect a better average response rate for $\mathcal{A}$ than for $\mathcal{B}$. This is quite an artificial example, but it demonstrates the danger of misleading results from randomised trials if heterogeneity is not carefully considered.

For this reason, the introductory question is how should we design a trial that is focused on a strategy comparison in the presence of such a heterogeneity of patient-drug-interaction if the relevant criteria in which the patients differ are not yet identified.

If we investigate the same strategy comparison as before, but change the randomisation process in such a way that the physicians decide between the therapy within each strategy and randomise patients to one strategy as was done in CUtLASS, the result of the trial depends on the physicians' decisions. Though the relevant criteria in which the patients differ are not yet identified, the physicians' decisions take the many particular characteristics of their patients into account. If we assume the best case that physicians allocate each patient to the right population, all patients treated with treatment $A_1$ come from population $P_1$ and have a response rate of 60%. In the same way, patients treated with $A_2$ will also have a response rate of 60%. In this trial, strategy $\mathcal{A}$ has an average response rate of 60% in total. Since we have no changes in response of patients treated with strategy $\mathcal{B}$, we obtain the superiority of strategy $\mathcal{A}$ over $\mathcal{B}$. This example shows that the idea of patient-oriented decisions can handle heterogeneity. However, it has some disadvantages when being implemented in the same way as in the CUtLASS study, e.g. selection bias, no representation of some treatments/comparisons and no progress of evidence, as mentioned in the previous section. Designs such as CUtLASS only perform as well as the physicians selecting the treatments. But the questions arise what are the challenges to its internal and external validity and how do we critically evaluate the results of such a trial (Schulz et al., 2016b).

## 1.4 Idea and goal

In this thesis, we define a new clinical trial design to solve the problems outlined above. 'The goal of the new design described here is to take an intermediate path combining the advantages of both study types [(RCT and CUtLASS)] by randomising treatment pairs in a first step, involving the investigators in deciding for a pair most appropriate to the patients' needs (described below) and then randomising the allocation [double-blinded] to one drug ([first-generation] or [second-generation antipsychotic]) of that chosen pair. Through this procedure, the new design should reflect everyday practice better than EUFEST and CATIE studies, as well as yielding more systematic comparisons than CUtLASS.'(Schulz et al., 2016a) To emphasise the combination of randomisation and patient-oriented decision, we called the new clinical trial design 'patient-oriented randomisation'. This study design compares strategies based on patient-oriented choice of physicians within each strategy to deal with the problem of heterogeneity. We assume that the knowledge of the physician about the patient and his medical history will lead to choices of a more effective treatment than purely randomised allocation within each strategy. Thus, the design reflects the daily clinical therapy practice without neglecting the basic methods to avoid bias—randomisation and blinding.

'The new design was implemented in the clinical trial "The Neuroleptic Strategy Study" (NeSSy) comparing efficacy and safety of the strategies using either first-generation or second-generation antipsychotics in patients suffering from schizophrenia. NeSSy was a multi-centre, double-blind study in which two first-generation antipsychotics and three second-generation antipsychotics were used. It was conducted from April 2010 to August 2013 at 20 clinical sites in Germany and was funded by the German Federal Ministry of Education and Research (BMBF).'(Schulz et al., 2016a)

The goal of this thesis is to investigate the new class of trial designs introduced firstly in the NeSSy study and to deduce general properties of this class. Only in a few sections, the NeSSy study is mentioned as an example.

CHAPTER 2

# Patient-oriented randomisation

## 2.1 Introduction

In the following section, the new trial design to compare strategies consisting of different treatments will be introduced. We start with a general definition of the randomisation process and describe every step with a random variable. Therefore, the considerations in this section concentrate on the properties of the design and the influence of the number of treatments on these properties. The decision how many treatments are selected in each strategy has far-reaching consequences and should be carefully considered during the planning phase of a clinical trial with this patient-oriented randomisation design.

## 2.2 Definition

**Definition 2.2.1 (Patient-oriented randomisation design for two strategies $\mathbf{POR}_{k,l}$).** *Let $\mathcal{A}$ and $\mathcal{B}$ be two different therapy strategies with any number of treatments $k$ in strategy $\mathcal{A}$ and $l$ in strategy $\mathcal{B}$. A patient-oriented randomisation design for two strategies $\mathrm{POR}_{k,l}$ is defined as study design containing two steps of randomisation and one patient-oriented decision of the physician in the following order:*

- *In the first step of randomisation, each patient is assigned two pairs of treatment, each pair consisting of one treatment of each strategy.*
- *In the patient-oriented step, the physician chooses one of the two previously randomised pairs.*
- *In the second step of randomisation, each patient is randomised to one of the two strategies $\mathcal{A}$ or $\mathcal{B}$, i.e. to the respective treatment of the selected pair.*

**Remark.**

- Thus, to enable the physician to take a patient-oriented decision, at least two treatments must be presented in one strategy. This design is symmetric in $k$ and $l$. Hence, without loss of generality, we assume $2 \leq l$ and $k \leq l$.
- The $\mathrm{POR}_{k,l}$ design was first implemented in the NeSSy study. The associated $\mathrm{POR}_{2,3}$ design is therefore called NeSSy design throughout this thesis.

**Notation.**

- The treatments in strategy $\mathcal{A}$ are denoted by $A_1, A_2, \ldots, A_k$ and the treatments in strategy $\mathcal{B}$ by $B_1, B_2, \ldots, B_l$.
- $\mathcal{A} = \{A_i \mid 1 \leq i \leq k\}$ and $\mathcal{B} = \{B_j \mid 1 \leq j \leq l,\ \max(2,k) \leq l\}$ are non-empty and countable sets. Therefore, the power sets $\mathcal{P}(\mathcal{A})$ and $\mathcal{P}(\mathcal{B})$ are $\sigma$-fields and the tuples $(\mathcal{A}, \mathcal{P}(\mathcal{A}))$ and $(\mathcal{B}, \mathcal{P}(\mathcal{B}))$ are measurable spaces.

**Example (Practical implementation).** For a better understanding of the practical implementation, we consider the case $k, l = 2$ as an example. Since we want to compare two different strategies, each treatment in $\mathcal{A}$ is compared to each treatment in $\mathcal{B}$. From the four treatments $A_1, A_2, B_1$ and $B_2$ the pairs

$$(A_1, B_1), \quad (A_1, B_2), \quad (A_2, B_1) \quad \text{and} \quad (A_2, B_2)$$

can be formed. In the first step of randomisation, two of these four pairs are randomly selected (random pair 1 and random pair 2). At this point, the physician chooses the most suitable of these two selected pairs for his patient according to efficacy and safety aspects. In the second randomisation step, the treatment strategy the patient is assigned to is chosen randomly. Consequently, the specific treatment for the patient is now determined. Neither patient nor physician know the result of the second randomisation step such that we have a double-blind randomisation. The randomisation process is illustrated by Figure 2.1.

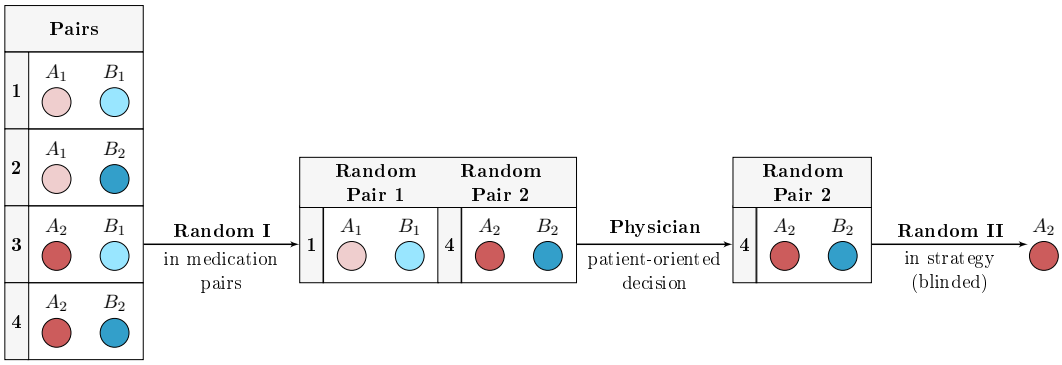



Figure 2.1: Randomisation scheme described by a hypothetical example for the $\text{POR}_{2,2}$ design.

## 2.3 Properties of $\text{POR}_{k,l}$

Some of the following properties are results from set theory and combinatorics and require no proof (see for example Georgii (2009)). For the other properties the proofs are given.

### 2.3.1 Pairs

**Property 2.3.1.** *Consider a* $\text{POR}_{k,l}$ *design and let* $\mathcal{A} \times \mathcal{B} = \{(A_i, B_j) \mid A_i \in \mathcal{A}, B_j \in \mathcal{B}\}$ *be the cartesian product between the two sets* $\mathcal{A}$ *and* $\mathcal{B}$*. If we denote the number of elements*

*in* $\mathcal{A} \times \mathcal{B}$ *by* $|\mathcal{A} \times \mathcal{B}|$*, then the number of pairs* $(A_i, B_j)$ *with* $i = 1, \ldots, k$*,* $j = 1, \ldots, l$ *and* $l \geq 2$ *in* $\mathcal{A} \times \mathcal{B}$ *is*

$$|\mathcal{A} \times \mathcal{B}| = |\mathcal{A}| \cdot |\mathcal{B}| = k \cdot l.$$

**Remark.** $\mathcal{A} \times \mathcal{B}$ is a non-empty and countable set. Therefore, $(\mathcal{A} \times \mathcal{B}, \mathcal{P}(\mathcal{A} \times \mathcal{B}))$ describes a measurable space.

### 2.3.2 Two-pair combination

**Definition 2.3.2 (Two-pair combination TPC).** *A two-pair combination* $\mathrm{TPC} = [(A_i, B_j), (A_{i'}, B_{j'})]$ *is defined as unordered pair of two randomly selected different pairs* $(A_i, B_j) \in \mathcal{A} \times \mathcal{B}$ *and* $(A_{i'}, B_{j'}) \in \mathcal{A} \times \mathcal{B} \setminus \{(A_i, B_j)\}$*. The set of all two-pair combinations is referred to as*

$$\begin{aligned}\mathcal{TPC}_{k,l} :=& (\mathcal{A} \times \mathcal{B}) \underset{k,l}{\times} (\mathcal{A} \times \mathcal{B}) \\ =& \{[\omega_1, \omega_2] \mid \omega_n \in \mathcal{A} \times \mathcal{B},\, n = 1, \ldots, |\mathcal{A} \times \mathcal{B}|; \omega_1 < \omega_2, \ldots, \omega_{|\mathcal{A} \times \mathcal{B}|}\}.\end{aligned}$$

*The operator '* $\underset{k,l}{\times}$ *' denotes the unordered cartesian product of* $\mathcal{A} \times \mathcal{B}$ *and* $\mathcal{A} \times \mathcal{B}$ *without the set of pairs with equal elements (drawing without replacement, unordered result).*

**Property 2.3.3.** *The number of all distinct two-pair combinations* $|\mathcal{TPC}_{k,l}|$ *in a* $\mathrm{POR}_{k,l}$ *design can be computed by*

$$|\mathcal{TPC}_{k,l}| := \binom{|\mathcal{A} \times \mathcal{B}|}{2} = \frac{kl(kl-1)}{2}.$$

**Remark.**

- $\mathcal{TPC}_{k,l}$ is a non-empty and countable set. Therefore, $(\mathcal{TPC}_{k,l}, \mathcal{P}(\mathcal{TPC}_{k,l}))$ describes a measurable space.
- The number of two-pair combinations is also symmetric but the sequence is quadratically increasing with the number of pairs. Therefore, it is not practicable to recommend a high number of therapies in both strategies. In Figure 2.2, the number of two-pair combinations are illustrated for different numbers of $k$ and $l$.

For a better understanding of what happened during the randomisation process, we define three different random variables, one for each of the step of Definition 2.2.1. All three random variables are discrete. The first random variable $\Gamma$ describes the first step of randomisation—the selection of one two-pair combination for each patient. The patient-oriented step is not really random, but we do not know all reasons the physicians take into account when choosing one pair of the two-pair combination based on the respective patient. We only see the distribution which describes the decision of the physicians between the two different pairs. The random variable $\Theta$ describes the distribution of the two different pairs in each two-pair combination. The third random variable $\Psi$ represents the second step of randomisation—the randomisation between the two different strategies $\mathcal{A}$ and $\mathcal{B}$.

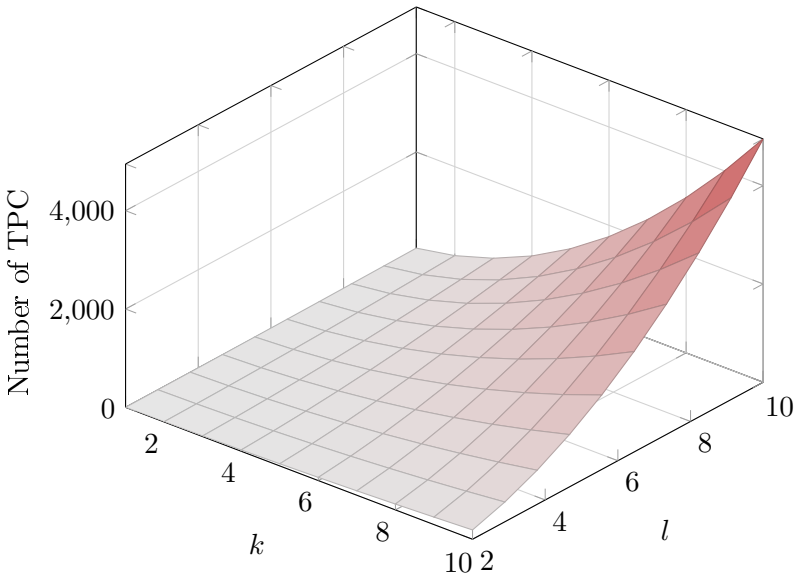



Figure 2.2: Number of two-pair combinations in a $\mathrm{POR}_{k,l}$ design.

**Definition 2.3.4 (Randomisation random variables).**

1. *Let* $\mathbb{P} : \mathcal{TPC}_{k,l} \to [0,1]$ *be the probability measure on* $(\mathcal{TPC}_{k,l}, \mathcal{P}(\mathcal{TPC}_{k,l}))$ *with* $\mathbb{P}(\{\mathrm{TPC}_m\}) = |\mathcal{TPC}_{k,l}|^{-1} = 2/(kl(kl-1))$ *for* $m = 1, \ldots, |\mathcal{TPC}_{k,l}|$.

   *Then the function*

   $$\Gamma : (\mathcal{TPC}_{k,l}, \mathcal{P}(\mathcal{TPC}_{k,l})) \longrightarrow (\mathcal{TPC}_{k,l}, \mathcal{P}(\mathcal{TPC}_{k,l}))$$

   *with the law* $\mathbb{P}_\Gamma$ *of* $\Gamma$ *under* $\mathbb{P}$ *is a random variable, which describes the randomisation in* $\mathcal{TPC}_{k,l}$. $\{\mathrm{TPC}_1, \ldots, \mathrm{TPC}_{|\mathcal{TPC}_{k,l}|}\}$ *is the support of* $\mathbb{P}_\Gamma$ *and*

   $$\mathbb{P}_\Gamma(\{\mathrm{TPC}_m\}) = \mathbb{P}\left(\{\mathrm{TPC}_m \mid \Gamma(\mathrm{TPC}_m) = \mathrm{TPC}_m\}\right) = \mathbb{P}(\Gamma = \mathrm{TPC}_m) = \frac{2}{kl(kl-1)}$$

   *are the single portabilities for* $m = 1, \ldots, |\mathcal{TPC}_{k,l}|$.

2. *The function*

   $$\Theta : (\mathcal{TPC}_{k,l}, \mathcal{P}(\mathcal{TPC}_{k,l})) \longrightarrow (\mathcal{A} \times \mathcal{B}, \mathcal{P}(\mathcal{A} \times \mathcal{B}))$$

   *with*

   $$\begin{aligned}
   \mathbb{P}_\Theta(\{\omega_n\}) &= \mathbb{P}\left(\{(\omega_1, \omega_2) \mid \Theta(\omega_1, \omega_2) = \omega_n,\ \omega_n \in \mathcal{A} \times \mathcal{B} \ \text{ for } \ n = 1, 2\}\right) \\
   &= \mathbb{P}(\Theta^{-1}(\omega_n),\ \omega_n \in \mathcal{A} \times \mathcal{B} \ \text{ for } \ n = 1, 2) \\
   &= \begin{cases} p_\Theta^m & \text{if } \Theta = \omega_1 = (A_i, B_j) \\ q_\Theta^m = (1 - p_\Theta^m) & \text{if } \Theta = \omega_2 = (A_{i'}, B_{j'}) \end{cases}
   \end{aligned}$$

   *for* $p_\Theta^m \in [0,1]$ *is a random variable which describes the distribution of the patient-oriented step of the randomisation procedure for each* $\mathrm{TPC}_m$, $m = 1, \ldots, |\mathcal{TPC}_{k,l}|$. $p_\Theta^m$ *describes the probability of the physician's decision for random pair* 1 *if the patient*

*receives the two-pair combination $m$.*

$$\Psi : (\mathcal{A} \times \mathcal{B},\, \mathcal{P}(\mathcal{A} \times \mathcal{B})) \longrightarrow (\mathcal{A} \cup \mathcal{B},\, \mathcal{P}(\mathcal{A} \cup \mathcal{B}))$$

*with*

$$\begin{aligned}\mathbb{P}_\Psi(\{C\}) &= \mathbb{P}(\{(A_i, B_j) \mid \Psi((A_i, \mathcal{B}_j)) = C,\, C \in \mathcal{A} \cup \mathcal{B}\}) \\ &= \mathbb{P}(\Psi^{-1}(C),\, C \in \mathcal{A} \cup \mathcal{B}\}) \\ &= \begin{cases} p_\Psi & \text{if } \Psi = C \in \mathcal{A} \\ q_\Psi = (1 - p_\Psi) & \text{if } \Psi = C \in \mathcal{B} \end{cases}\end{aligned}$$

*for $p_\Psi \in [0, 1]$ is a random variable which randomises each pair $(A_i, B_j) \in \mathcal{A} \times \mathcal{B}$ to one strategy (either strategy $\mathcal{A}$ with treatment $A_i$ or strategy $\mathcal{B}$ with treatment $B_j$). $p_\Psi$ describes the probability for a patient receiving a treatment of strategy $A$.*

**Remark.**

1. The random variable $\Psi$ is independent of $\Theta$.
2. The superposition of the three random variables $\Gamma$, $\Psi$ and $\Theta$ describes all possible outcomes of the randomisation process.
3. The probability of $\Psi$ resulting as an element of $\mathcal{A}$ or $\mathcal{B}$ is depending on the sampling strategy. In most cases it will be chosen as $p_\Psi = 1/2$, which is implicitly assumed in the course of this thesis. Of course in general sampling for strategies like one-to-two are possible if the study goal demands such unequal randomisation.

**Notation.**

- To receive a better understanding of the possibilities of the physicians' decision we consider the realisation of the first and second randomisation step without the patient-oriented decision step. That means that if we have one two-pair combination $[(A_i, B_j),(A_{i'}, B_{j'})]$, we only consider the corresponding $\mathcal{A}$-pair $(A_i, A_{i'})$ and the corresponding $\mathcal{B}$-pair $(B_j, B_{j'})$. Since we are not interested in the order of this pairs we summarise all pairs with the same elements in one equivalence class of unordered pairs $[A_i, A_{i'}] = \{(A_i, A_{i'}),(A_{i'}, A_i)\}$ and analogous for $[B_j, B_{j'}] = \{(B_j, B_{j'}),(B_{j'}, B_j)\}$. The set of all unordered equivalence classes of $\mathcal{A}$-pairs is denoted by

$$\mathcal{A} \underset{k,l}{\otimes} \mathcal{A} := \{[A_i, A_{i'}] \mid A_i, A_{i'} \in \mathcal{A}\}$$

  and analogous the set of all unordered equivalence classes of $\mathcal{B}$-pairs by

$$\mathcal{B} \underset{k,l}{\otimes} \mathcal{B} := \{[B_i, B_{i'}] \mid B_i, B_{i'} \in \mathcal{B}\}.$$

  The operator '$\underset{k,l}{\otimes}$' denotes the unordered cartesian product of $\mathcal{A}$ and $\mathcal{A}$ as well as $\mathcal{B}$ and $\mathcal{B}$.

- Therefore, we also define two random variables $\Psi_\mathcal{A}$ and $\Psi_\mathcal{B}$ to receive all corresponding unordered $\mathcal{A}$-pairs and $\mathcal{B}$-pairs and the probabilities of pairs with equal and mixed elements. The function $\Psi_\mathcal{A}$ is defined as

$$\Psi_\mathcal{A} : (\mathcal{TPC}_{k,l},\, \mathcal{P}(\mathcal{TPC}_{k,l})) \longrightarrow (\mathcal{A} \underset{k,l}{\otimes} \mathcal{A},\, \mathcal{P}(\mathcal{A} \underset{k,l}{\otimes} \mathcal{A}))$$

with

$$\begin{aligned}\mathbb{P}_{\Psi_{\mathcal{A}}}(\{[A_i, A_{i'}]\}) &= \mathbb{P}(\Psi_{\mathcal{A}}^{-1}([A_i, A_{i'}]),\, A_i, A_{i'} \in \mathcal{A}\}) \\ &= \begin{cases} p_{\mathcal{A}} & \text{if } A_i = A_{i'} \\ q_{\mathcal{A}} & \text{if } A_i \neq A_{i'} \end{cases}\end{aligned}$$

for $p_{\mathcal{A}}, q_{\mathcal{A}} \in [0,1]$ and the function $\Psi_{\mathcal{B}}$ is defined as

$$\Psi_{\mathcal{B}} : (\mathcal{TPC}_{k,l},\, \mathcal{P}(\mathcal{TPC}_{k,l})) \longrightarrow (\underset{k,l}{\mathcal{B} \otimes} \mathcal{B},\, \mathcal{P}(\underset{k,l}{\mathcal{B} \otimes} \mathcal{B}))$$

with

$$\begin{aligned}\mathbb{P}_{\Psi_{\mathcal{B}}}(\{[B_j, B_{j'}]\}) &= \mathbb{P}(\Psi_{\mathcal{B}}^{-1}([B_j, B_{j'}]),\, B_j, B_{j'} \in \mathcal{B}\}) \\ &= \begin{cases} p_{\mathcal{B}} & \text{if } B_j = B_{j'} \\ q_{\mathcal{B}} & \text{if } B_j \neq B_{j'} \end{cases}.\end{aligned}$$

for $p_{\mathcal{B}}, q_{\mathcal{B}} \in [0,1]$. We will determine the probabilities $p_{\mathcal{A}}, p_{\mathcal{B}}$ and $q_{\mathcal{A}}, q_{\mathcal{B}}$ in the following Subsections 2.3.3 and 2.3.4.

**Remark.** To show how the different random variables introduced above are connected, we give a graphical representation in the following diagram (Figure 2.3).

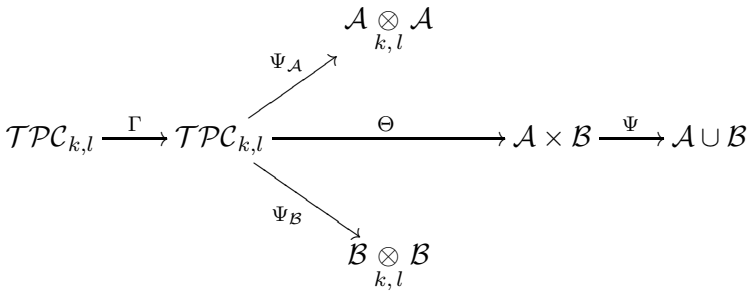



Figure 2.3: Interaction of random variables involved in the $\text{POR}_{k,l}$ design.

**Example.** In Table 2.1, we find all possible two-pair combinations from the $\text{POR}_{2,2}$ design. The physician receives one of these two-pair combinations at random, for example two-pair combination 3 for one patient. Let us assume that this patient does not tolerate the drug $B_2$. Hence, the physician chooses random pair 1. This underlines that the $\text{POR}_{k,l}$ design offers the opportunity for patient-oriented choices.

The allocation of each patient to one of the strategies is random and independent of the physician's choice. However, the physician takes the consideration about what happens if the patient is randomised to strategy $\mathcal{A}$ as well as $\mathcal{B}$ into account. For example, consider the first two-pair combination of Table 2.1 above. If the patient is randomised to strategy $\mathcal{A}$, he receives treatment $A_1$ independent of the choice of the physician. Hence, the physician is focused on the treatments of strategy $\mathcal{B}$. He has to decide whether treatment $B_1$ or $B_2$ is better for the respective patient. In this case, the physician's selection of one random

| Number of two-pair combination | $\mathcal{TPC}_{2,2}$ | | Equivalence class in | |
|---|---|---|---|---|
| | Random pair 1 | Random pair 2 | $A \underset{2,2}{\otimes} \mathcal{A}$ | $\mathcal{B} \underset{2,2}{\otimes} \mathcal{B}$ |
| 1 | $(A_1, B_1)$ | $(A_1, B_2)$ | $[A_1, A_1]$ | $[B_1, B_2]$ |
| 2 | $(A_1, B_1)$ | $(A_2, B_1)$ | $[A_1, A_2]$ | $[B_1, B_1]$ |
| 3 | $(A_1, B_1)$ | $(A_2, B_2)$ | $[A_1, A_2]$ | $[B_1, B_2]$ |
| 4 | $(A_1, B_2)$ | $(A_2, B_1)$ | $[A_1, A_2]$ | $[B_2, B_1]$ |
| 5 | $(A_1, B_2)$ | $(A_2, B_2)$ | $[A_1, A_2]$ | $[B_2, B_2]$ |
| 6 | $(A_2, B_1)$ | $(A_2, B_2)$ | $[A_2, A_2]$ | $[B_1, B_2]$ |

Table 2.1: Two-pair combinations of the $\mathrm{POR}_{2,2}$ design. The identical treatments in a two-pair combination are highlighted.

pair can be interpreted as a clear decision for either treatment $B_1$ or treatment $B_2$. The last two columns of Table 2.1 describe this consideration for all two-pair combinations

$$\mathcal{A} \underset{2,2}{\otimes} \mathcal{A} = \{[A_1, A_1],[A_1, A_2],[A_2, A_2]\}$$
$$\mathcal{B} \underset{2,2}{\otimes} \mathcal{B} = \{[B_1, B_1],[B_1, B_2],[B_2, B_2]\}.$$

In four out of all six two-pair combinations, we have either an identical treatment in strategy $\mathcal{A}$ or $\mathcal{B}$. Such two-pair combinations are called informative combinations. These informative combinations are of particular interest. We can conclude from the physician's decision which concrete treatment he prefers for the respective patients. Therefore, we take a closer look at these two-pair combinations in the next section.

### 2.3.3 Informative combination

**Definition 2.3.5 (Identical and mixed pairs).** *A corresponding unordered pair of a two-pair combination is called*

1. *identical, if the treatments in the unordered pair are the same, i.e.* $[C_i, C_i]$ *for* $C_i \in \mathcal{A}$ *or* $C_i \in \mathcal{B}$*;*
2. *mixed, if the treatments in the unordered pair are not the same, i.e.* $[C_i, C_{i'}]$ *for* $i \neq i'$ *and* $C_i, C_{i'} \in \mathcal{A}$ *or* $C_i, C_{i'} \in \mathcal{B}$*.*

**Definition 2.3.6 (Informative combination).** *An informative combination is defined as a two-pair combination where either the corresponding unordered* $\mathcal{A}$*-pair or* $\mathcal{B}$*-pair is identical. To illustrate in which strategy treatments are identical and in which strategy we found the information, the informative combinations are called* $\mathcal{A}$*-informative combination if the corresponding* $\mathcal{B}$*-pair is identical as well as* $\mathcal{B}$*-informative combination if the corresponding* $\mathcal{A}$*-pair is identical.*

**Property 2.3.7.**

- *In a* $\mathrm{POR}_{k,l}$ *design, there are* $k$ *distinct identical* $\mathcal{A}$*-pairs and for* $k > 1$ *there are* $l$ *distinct identical* $\mathcal{B}$*-pairs.*

- *For each identical $\mathcal{A}$-pair $[A_i, A_i]$ in $\mathcal{A}^{\otimes}_{k,l}\mathcal{A}$ the pre-image $\Psi^{-1}_{\mathcal{A}}([A_i, A_i])$ consists of $l(l-1)/2$ two-pair combinations and for each identical $\mathcal{B}$-pairs $[B_j, B_j]$ in $\mathcal{B}^{\otimes}_{k,l}\mathcal{B}$ the pre-image $\Psi^{-1}_{\mathcal{B}}([B_j, B_j])$ consists of $k(k-1)/2$ two-pair combinations.*

**Remark.**

- For $k = 1$, $\mathcal{A}^{\otimes}_{1,l}\mathcal{A} = \{[A_1, A_1]\}$ consist of one identical $\mathcal{A}$-pair. In $\mathcal{B}^{\otimes}_{1,l}\mathcal{B}$ there is no identical $\mathcal{B}$-pair.
- For $k \neq 1$, the number of pre-images of identical $\mathcal{A}$-pairs for one treatment $A_i$ depends on the number of treatments in $\mathcal{B}$ and vice versa.
- The probability $p_{\mathcal{A}}$ for two-pair combinations with one identical $\mathcal{A}$-pair is calculated by the ratio of the number of pre-images of the identical $\mathcal{A}$-pair and the number of two-pair combinations, i.e.

$$p_{\mathcal{A}} = \mathbb{P}\left(\Psi_A^{-1}([A_i, A_i])\right) = \frac{|\Psi_{\mathcal{A}}^{-1}([A_i, A_i])|}{|\mathcal{TPC}_{k,l}|} = \frac{l-1}{k(kl-1)} \tag{2.1}$$

  for $i = 1, \ldots, k$, and the probability $p_{\mathcal{B}}$ for two-pair combinations with one identical $\mathcal{B}$-pair is calculated by

$$p_{\mathcal{B}} = \mathbb{P}\left(\Psi_B^{-1}([B_i,B_i])\right) = \frac{|\Psi_{\mathcal{B}}^{-1}([B_j, B_j])|}{|\mathcal{TPC}_{k,l}|} = \frac{k-1}{l(kl-1)} \tag{2.2}$$

  for $j = 1, \ldots, l$.

**Notation.** The proofs of the following properties often use a sequence indexed by two parameters. In the applications one of them is constant. Therefore, we introduce an abbreviation for the sequence $(a_{k,l})_{k\in\mathbb{N}\setminus\{1\}, l\in\mathbb{N}\setminus\{1\}}$ with $k$ or $l$ constant. If the number of treatments in one strategy is fixed, the associated parameter is replaced by a dot, i.e. $(a_{k,.})_{k\in\mathbb{N}\setminus\{1\}}$ for $l = const.$ and $(a_{.,l})_{l\in\mathbb{N}\setminus\{1\}}$ for $k = const.$

**Property 2.3.8.**

1. *Consider the probability for identical $\mathcal{A}$-pairs as a sequence*

$$(a_{k,l})_{k\in\mathbb{N}\setminus\{1\}, l\in\mathbb{N}\setminus\{1\}} := \frac{l-1}{k(kl-1)},$$

   *in $k$ and $l$. Then the sequence $(a_{.,l})_{l\in\mathbb{N}\setminus\{1\}}$ is monotonically increasing for $k = const.$ and convergent to $1/k^2$. For $l = const.$, the sequence $(a_{k,.})_{k\in\mathbb{N}\setminus\{1\}}$ is monotonically decreasing and convergent to 0.*

2. *Similarly, consider the probability for identical $\mathcal{B}$-pairs as a sequence*

$$(b_{k,l})_{k\in\mathbb{N}\setminus\{1\}\, l\in\mathbb{N}\setminus\{1\}} := \frac{k-1}{l(kl-1)}.$$

   *Then, the sequence $(b_{.,l})_{l\in\mathbb{N}\setminus\{1\}}$ is monotonically decreasing for $k = const.$ and convergent to 0. For $l = const.$, the sequence $(b_{k,.})_{k\in\mathbb{N}\setminus\{1\}}$ is monotonically increasing and convergent to $1/l^2$.*

**Example.** In Figure 2.4, we can see the probabilities for identical $\mathcal{A}$-pairs and for identical $\mathcal{B}$-pairs for different numbers of treatments $k$ and $l$.

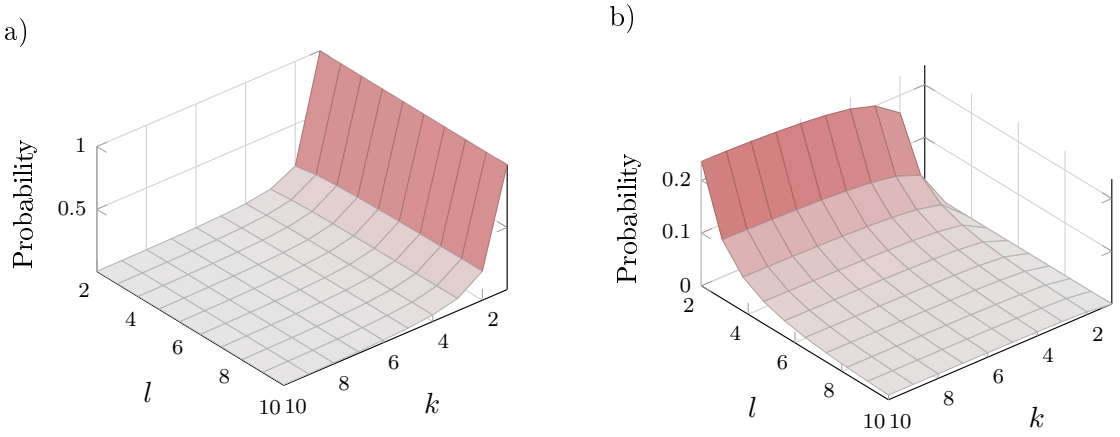



Figure 2.4: Probability for identical a) $\mathcal{A}$-pairs and b) $\mathcal{B}$-pairs in a $\mathrm{POR}_{k,l}$ design.

The properties of the patient-oriented randomisation design depend on $k$ and $l$. In order to not always check the monotonicity and the convergence of the resulting sequences of probabilities we consider the general case in the following lemma.

**Lemma 2.3.9.** *Let*

$$(a_n)_{n\in\mathbb{N}\setminus\{1\}} := \frac{\alpha n+\beta}{\gamma n^2+\delta n+\varepsilon}$$

*a real valued sequence with $\alpha$, $\beta$, $\gamma$, $\delta$, $\varepsilon \in \mathbb{R}$ and $\alpha$, $\gamma \geq 0$. Let also $\alpha n+\beta \geq 0$ as well as $\gamma n^2+\delta n+\varepsilon > 0$ for all $n \in \mathbb{N}\setminus\{1\}$. Then*

1. *For $\gamma = 0$, $\delta > 0$, the sequence is convergent to $\alpha/\delta$.*
   - 1.1 *If $\beta\delta < \alpha\varepsilon$, then $(a_n)_{n\in\mathbb{N}\setminus\{1\}}$ is strictly monotonically increasing.*
   - 1.2 *If $\beta\delta > \alpha\varepsilon$, then $(a_n)_{n\in\mathbb{N}\setminus\{1\}}$ is strictly monotonically decreasing.*
2. *For $\gamma \neq 0$,*
   - 2.1 *$\alpha = 0$ and $\beta > 0$, $(a_n)_{n\in\mathbb{N}\setminus\{1\}}$ is convergent to 0 and strictly monotonically decreasing for all $n > \max(1, -1/2-\delta/\gamma)$.*
   - 2.2 *$\alpha \neq 0$, $(a_n)_{n\in\mathbb{N}\setminus\{1\}}$ is convergent to 0 and is strictly monotonically decreasing for $n \geq \max(-\beta/\alpha,\, N(\alpha,\beta,\gamma,\delta,\varepsilon))$ with*

$$N(\alpha,\beta,\gamma,\delta,\varepsilon) = -\frac{1}{2}-\frac{\beta}{\alpha}+\sqrt{\frac{1}{4}+\frac{\beta^2}{\alpha^2}-\frac{\beta\delta}{\alpha\gamma}+\frac{\varepsilon}{\gamma}} \tag{2.3}$$

*if $N$ exists, (i.e. the discriminant is greater than or equal zero), and otherwise for $n \geq -\beta/\alpha$.*

*Proof (of Lemma 2.3.9).*

1. Let $\gamma = 0$. Consider

$$a_n - \frac{\alpha}{\delta} = \frac{\alpha n + \beta}{\delta n + \varepsilon} - \frac{\alpha}{\delta} = \frac{\beta\delta - \alpha\varepsilon}{\delta^2 n + \delta\varepsilon} \underset{n\to\infty}{\longrightarrow} 0. \tag{2.4}$$

Therefore, the sequence $(a_n)_{n\in\mathbb{N}\setminus\{1\}}$ is convergent to $\alpha/\delta$.

1.1 Suppose $\beta\delta < \alpha\varepsilon$. To show that $(a_n)_{n\in\mathbb{N}\setminus\{1\}}$ is strictly monotonically increasing, we establish $a_{n+1} > a_n$ for all $n \in \mathbb{N} \setminus \{1\}$. From Equation (2.4), we obtain

$$\begin{aligned} & a_n < a_{n+1} \\ \Leftrightarrow \quad & a_n - \frac{\alpha}{\delta} < a_{n+1} - \frac{\alpha}{\delta} \\ \Leftrightarrow \quad & \frac{\beta\delta - \alpha\varepsilon}{\delta^2 n + \delta\varepsilon} < \frac{\beta\delta - \alpha\varepsilon}{\delta^2(n+1) + \delta\varepsilon}. \end{aligned}$$

Which is a true statement, since $\beta\delta - \alpha\varepsilon < 0$ and $\delta^2 n + \delta\varepsilon < \delta^2(n+1) + \delta\varepsilon$ for $\delta > 0$ and $\delta n + \varepsilon > 0$. Hence, $(a_n)_{n\in\mathbb{N}\setminus\{1\}}$ is strictly monotonically increasing.

1.2 If $\beta\delta > \alpha\varepsilon$, it can be shown analogously to 1.1 that $(a_n)_{n\in\mathbb{N}\setminus\{1\}}$ is strictly monotonically decreasing.

2. First, we prove the monotonicity of $(a_n)_{n\in\mathbb{N}\setminus\{1\}}$. The sequence is strictly monotonically decreasing if $a_n > a_{n+1}$ for all $n \in \mathbb{N} \setminus \{1\}$.

$$\begin{aligned} & a_n > a_{n+1} \\ \Leftrightarrow \quad & \frac{\alpha n + \beta}{\gamma n^2 + \delta n + \varepsilon} > \frac{\alpha(n+1) + \beta}{\gamma(n+1)^2 + \delta(n+1) + \varepsilon} \\ \Leftrightarrow \quad & (\alpha n + \beta)(\gamma n^2 + 2\gamma n + \gamma + \delta n + \delta + \varepsilon) > (\alpha n + \alpha + \beta)(\gamma n^2 + \delta n + \varepsilon) \\ \Leftrightarrow \quad & \alpha\gamma n^3 + 2\alpha\gamma n^2 + \alpha\gamma n + \alpha\delta n^2 + \alpha\delta n + \alpha\varepsilon n > \alpha\gamma n^3 + \alpha\delta n^2 + \alpha\varepsilon n + \alpha\gamma n^2 + \alpha\delta n \\ & \quad + \beta\gamma n^2 + 2\beta\gamma n + \beta\gamma + \beta\delta n + \beta\delta + \beta\varepsilon \qquad + \alpha\varepsilon + \beta\gamma n^2 + \beta\delta n + \beta\varepsilon \\ \Leftrightarrow \quad & \alpha\gamma n^2 + (\alpha\gamma + 2\beta\gamma)n + \beta\gamma + \beta\delta - \alpha\varepsilon > 0. \end{aligned} \tag{2.5}$$

2.1 Let $\alpha = 0$. Then Equation (2.5) becomes

$$\begin{aligned} & 2\beta\gamma n + \beta\gamma + \beta\delta > 0 \\ \Leftrightarrow \quad & n > -\frac{1}{2} - \frac{\delta}{\gamma}, \end{aligned} \tag{2.6}$$

for $\beta > 0$. Hence, the sequence is strictly monotonically decreasing for all $n > \max(1, -1/2 - \delta/\gamma)$.

Since both the numerator and the denominator of $(a_n)_{n\in\mathbb{N}\setminus\{1\}}$ are positive, the sequence is clearly bounded from below by 0. The sequence is convergent because we have proved that $(a_n)_{n\in\mathbb{N}\setminus\{1\}}$ is monotonically decreasing and bounded

from below. Finally, the limit can be computed by

$$\lim_{n\to\infty} \frac{\beta}{\gamma n^2 + \delta n + \varepsilon} = \lim_{n\to\infty} \frac{\frac{\beta}{n^2}}{\gamma + \frac{\delta}{n} + \frac{\varepsilon}{n^2}} = 0.$$

2.2 Let $\alpha \neq 0$, then the left side of inequality (2.5) is a quadratic polynomial in $n$ with a positive leading coefficient. Therefore, the inequality (2.5) is always true if the quadratic equation has no roots, or when $n$ is greater or equal than the largest root $N(\alpha, \beta, \gamma, \delta, \varepsilon)$ given by (2.3).

To prove convergence, it suffices again to show that the sequence is bounded from below by 0.

$$\begin{aligned}
& a_n \geq 0 \\
\Leftrightarrow \quad & \frac{\alpha n + \beta}{\gamma n^2 + \delta n + \varepsilon} \geq 0 \\
\Leftrightarrow \quad & \alpha n + \beta \geq 0, \text{ since } \quad \gamma n^2 + \delta n + \varepsilon > 0 \\
\Leftrightarrow \quad & n \geq -\frac{\beta}{\alpha}.
\end{aligned}$$

Hence, the sequence $(a_n)_{n\in\mathbb{N}\setminus\{1\}}$ is convergent and the limit is

$$\lim_{n\to\infty} \frac{\alpha n + \beta}{\gamma n^2 + \delta n + \varepsilon} = \lim_{n\to\infty} \frac{\frac{\alpha}{n} + \frac{\beta}{n^2}}{\gamma + \frac{\delta}{n} + \frac{\varepsilon}{n^2}} = 0. \qquad \square$$

*Proof (of Property 2.3.8).*

1. Let us consider the sequence

$$(a_{.,l})_{l\in\mathbb{N}\setminus\{1\}} = \frac{l-1}{k^2 l - k}$$

which can be obtained from $(a_n)_{n\in\mathbb{N}\setminus\{1\}}$ of Lemma 2.3.9 with $n = l$, $\alpha = 1$, $\beta = -1$, $\gamma = 0$, $\delta = k^2$ and $\varepsilon = -k$. To show the claim, we only have to prove the condition $\beta\delta < \alpha\varepsilon$. Since

$$\beta\delta < \alpha\varepsilon \quad \Leftrightarrow \quad -k^2 < -k,$$

the sequence increases strictly monotonically and converges to $\alpha/\delta = 1/k^2$.

For $l = const.$ we consider the sequence $(a_{k,.})_{k\in\mathbb{N}\setminus\{1\}}$ with a quadratic denominator in $k$ and $\alpha = 0$,

$$(a_{k,.})_{k\in\mathbb{N}\setminus\{1\}} = \frac{l-1}{lk^2 - k},$$

which can be obtained from $(a_n)_{n\in\mathbb{N}\setminus\{1\}}$ of Lemma 2.3.9 with $n = k$, $\beta = l-1$, $\gamma = l$, $\delta = -1$ and $\varepsilon = 0$. Since $-1/2 - \delta/\gamma = -1/2 + 1/l \leq 0 < k$ and $\beta = l - 1 \geq 0$, the condition (2.6) in the proof of Lemma 2.3.9 is satisfied and the sequence $(a_{k,.})_{k\in\mathbb{N}\setminus\{1\}}$ is strictly monotonically decreasing and convergent to 0.

2. Analogously to strategy $\mathcal{A}$ we can consider the sequence $(b_{.,l})_{l\in\mathbb{N}\setminus\{1\}}$ and $(b_{k,.})_{k\in\mathbb{N}\setminus\{1\}}$ and prove the conditions in Lemma 2.3.9. □

**Example.**

1. For the $\text{POR}_{2,2}$ design, the $\mathcal{B}$-informative combinations can be seen in line 1 and 6 of Table 2.1 with the corresponding identical $\mathcal{A}$-pairs $[A_1, A_1]$ and $[A_2, A_2]$. The $\mathcal{A}$-informative combinations can be seen in line 2 and 5 of Table 2.1 with the corresponding identical $\mathcal{B}$-pairs $[B_1, B_1]$ and $[B_2, B_2]$. Each identical pair has a probability of $p_{\mathcal{A}} = p_{\mathcal{B}} = 1/6$.

2. Suppose $k = 2$. Then the probability for identical $\mathcal{A}$-pairs increases and converges to $1/k^2 = 1/4$ and the probability for identical $\mathcal{B}$-pairs decreases for increasing $l$ and converges to 0 (see Figure 2.5). In general, the probability of identical pairs in one strategy can be increased when the number of treatments in this strategy is constant while the number of treatments in the remaining strategy increases. This connection is important for later considerations.

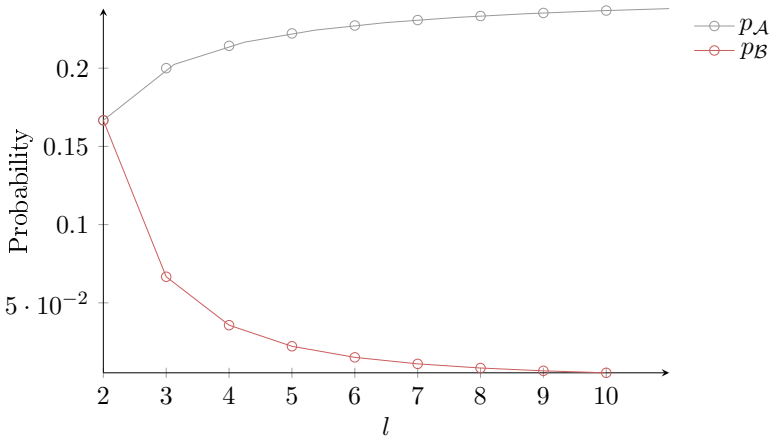



Figure 2.5: Probability for identical $\mathcal{A}$-pairs $p_{\mathcal{A}}$ and for identical $\mathcal{B}$-pairs $p_{\mathcal{B}}$ in a $\text{POR}_{2,l}$ design.

### 2.3.4 Mixed combination

**Definition 2.3.10 (Mixed combination).** *A mixed combination is defined as a two-pair combination $[(A_i, B_j),(A_{i'}, B_{j'})]$ where the corresponding unordered $\mathcal{A}$-pair and the corresponding unordered $\mathcal{B}$-pair are mixed, i.e. $A_i \neq A_{i'}$ and $B_j \neq B_{j'}$.*

**Notation.** An $\mathcal{A}$-pair with two different treatments or a $\mathcal{B}$-pair with two different treatments are denoted by mixed $\mathcal{A}$-pair or mixed $\mathcal{B}$-pair respectively.

**Property 2.3.11.**

- *In a $\text{POR}_{k,l}$ design, there are $k(k-1)/2$ distinct mixed $\mathcal{A}$-pairs and $l(l-1)/2$ distinct mixed $\mathcal{B}$-pairs.*

- *In the case of a* $\mathrm{POR}_{k,l}$ *design with* $k \neq 1$*, the number of pre-images of a mixed* $\mathcal{A}$*-pair* $\Psi_{\mathcal{A}}^{-1}([A_i, A_{i'}])$ *is equal to* $l^2$ *and the number of pre-images of a mixed* $\mathcal{B}$*-pair* $\Psi_{\mathcal{B}}^{-1}([B_j, B_{j'}])$ *is equal to* $k^2$*. For the special case* $k = 1$*, there are no mixed* $\mathcal{A}$*-pairs and the number of pre-images of a mixed* $\mathcal{B}$*-pair corresponds to the number of two-pair combinations* $l(l-1)/2$*.*

**Remark.**

- For $k \neq 1$, the number of mixed $\mathcal{A}$-pairs depends on the number of treatments in $\mathcal{B}$ and the number of mixed $\mathcal{B}$-pairs depends on the number of treatments in $\mathcal{A}$.
- The probability $q_{\mathcal{A}}$ for mixed $\mathcal{A}$-pairs is

$$q_{\mathcal{A}} = \mathbb{P}\left(\Psi_A^{-1}([A_i, A_{i'}])\right) = \frac{|\Psi_{\mathcal{A}}^{-1}([A_i, A_{i'}])|}{|\mathcal{TPC}_{k,l}|} = \begin{cases} \frac{2l}{k(kl-1)} & \text{if } k > 1 \\ 0 & \text{if } k = 1 \end{cases} \tag{2.7}$$

  for $i, i' = 1, \ldots, k$ and $i \neq i'$, and the probability $q_{\mathcal{B}}$ for mixed $\mathcal{B}$-pairs is

$$q_{\mathcal{B}} = \mathbb{P}\left(\Psi_B{-}1([B_j, B_{j'}])\right) = \frac{|\Psi_{\mathcal{B}}^{-1}([B_i,B_{i'}])|}{|\mathcal{TPC}_{k,l}|} = \begin{cases} \frac{2k}{l(kl-1)} & \text{if } k > 1 \\ 1 & \text{if } k = 1 \end{cases} \tag{2.8}$$

  for $j, j' = 1, \ldots, l$ and $j \neq j'$.

**Property 2.3.12.**

1. *We consider the probability for mixed* $\mathcal{A}$*-pairs as a sequence*

$$(a_{k,l})_{k \in \mathbb{N}\setminus\{1\}, l \in \mathbb{N}\setminus\{1\}} := \frac{2l}{k(kl-1)},$$

   *in* $k$ *and* $l$*. Then the sequence* $(a_{.,l})_{l \in \mathbb{N}\setminus\{1\}}$ *is strictly monotonically decreasing to* $2/k^2$ *when* $k$ *is constant. For* $l = const.$*, the sequence* $(a_{k,.})_{k \in \mathbb{N}\setminus\{1\}}$ *is strictly monotonically decreasing and convergent to* $0$*.*

2. *Analogously, we consider the probability for mixed* $\mathcal{B}$*-pairs as sequence*

$$(b_{k,l})_{k \in \mathbb{N}\setminus\{1\}, l \in \mathbb{N}\setminus\{1\}} := \frac{2k}{l(kl-1)}.$$

   *Then the sequence* $(b_{.,l})_{l \in \mathbb{N}\setminus\{1\}}$ *the is strictly monotonically decreasing for* $k = const.$ *and convergent to* $0$*. For* $l = const.$*, the sequence* $(b_{k,.})_{k \in \mathbb{N}\setminus\{1\}}$ *is strictly monotonically decreasing and convergent to* $2/l^2$*.*

*Proof.*

1. For $k = const.$, the denominator of the sequence

$$(a_{.,l})_{l \in \mathbb{N}\setminus\{1\}} = \frac{2l}{k^2 l - k}$$

   which can be obtained from $(a_n)_{n \in \mathbb{N}\setminus\{1\}}$ of Lemma 2.3.9 with $n = l$, $\alpha = 2$, $\beta = 0$, $\gamma = 0$, $\delta = k^2$ and $\varepsilon = -k$ is affine linear in $l$. With the help of Lemma 2.3.9, we

know that $(a_{\cdot,l})_{l\in\mathbb{N}\setminus\{1\}}$ is convergent to $\alpha/\delta = 2/k^2$. For the monotonicity behaviour we prove the relationship of $\beta\delta = 0$ and $\alpha\varepsilon = -2k$ and receive $\beta\delta > \alpha\varepsilon$. Hence, $(a_{\cdot,l})_{l\in\mathbb{N}\setminus\{1\}}$ is strictly monotonically decreasing.

For $l = const.$, the denominator of the sequence is a quadratic polynomial in $k$ and can be obtained from $(a_n)_{n\in\mathbb{N}\setminus\{1\}}$ of Lemma 2.3.9 with $n = k$, $\alpha = 0$, $\beta = 2l$,$\gamma = l$, $\delta = -1$ and $\varepsilon = 0$. Since $\beta > 0$, we only have to prove that $k > \max(1, -1/2-\delta/\gamma)$. With $\gamma = 2l$ and $\delta = -1$, we obtain $-1/2 + 1/(2l) < 1 < k$. By Lemma 2.3.9, the sequence is strictly monotonically decreasing and convergent to 0.

2. The results are obtained by symmetry from 1, because

$$(a_{k,l})_{k\in\mathbb{N}\setminus\{1\},\, l\in\mathbb{N}\setminus\{1\}} = \frac{2k}{l(lk-1)} = (b_{l,k})_{l\in\mathbb{N}\setminus\{1\},\, k\in\mathbb{N}\setminus\{1\}}\,. \qquad \square$$

**Example.**

1. In Figure 2.6, we can see the probabilities for mixed $\mathcal{A}$-pairs and for mixed $\mathcal{B}$-pairs for different numbers of treatments $k$ and $l$.

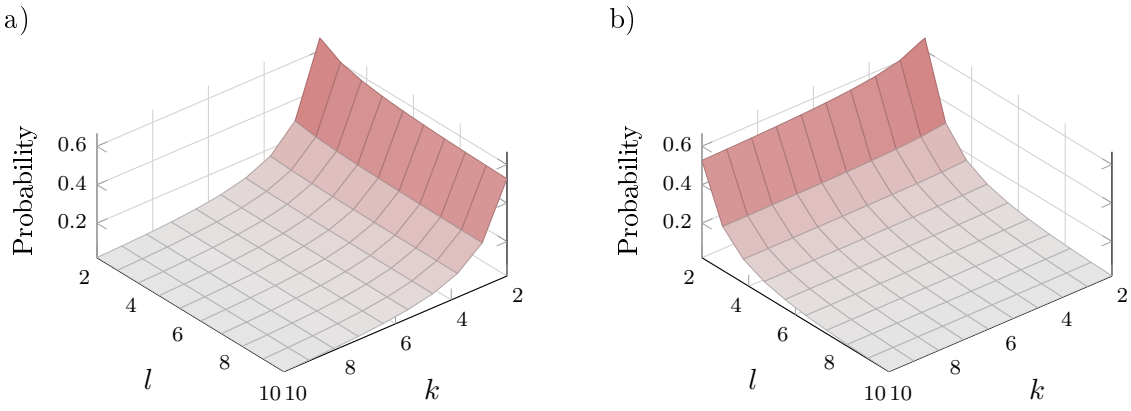



Figure 2.6: Probability for mixed a) $\mathcal{A}$-pairs and b) $\mathcal{B}$-pairs in a $\mathrm{POR}_{k,l}$ design.

2. For a $\mathrm{POR}_{2,2}$ design, the number of pre-images of the only mixed $\mathcal{A}$-pair $[A_1, A_2]$ is four. Analogously, we find one mixed $\mathcal{B}$-pair $[B_1, B_2]$ for which the number of pre-images is also four. Therefore, the probability for mixed $\mathcal{A}$-pairs or $\mathcal{B}$-pairs is $q_{\mathcal{A}} = q_B = 4/6 = 2/3$ in a $\mathrm{POR}_{2,2}$ design.

3. Consider $k = 2$, the probability for mixed $\mathcal{A}$-pairs decreases and converges to $1/2$ and the probability for mixed $\mathcal{B}$-pairs decreases and converges to 0 (see Figure 2.7). As we have also seen in Figure 2.5, the probabilities change much more in the strategy where we add one or more treatments as in the other strategy with a constant number of treatments.

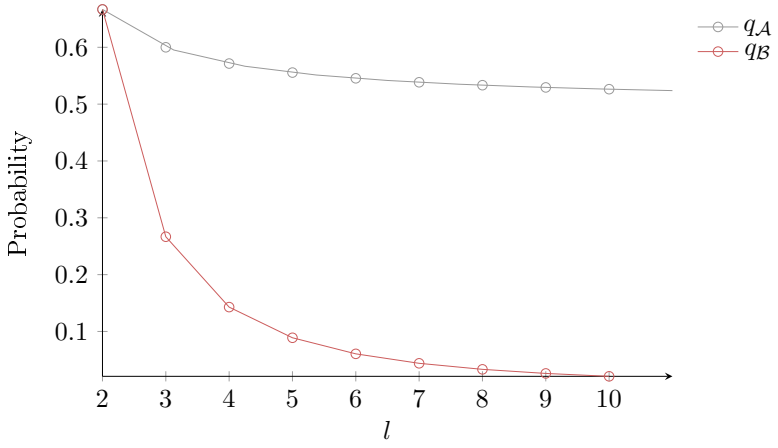



Figure 2.7: Probability for mixed $\mathcal{A}$-pairs $q_{\mathcal{A}}$ and $\mathcal{B}$-pairs $q_{\mathcal{B}}$ in a $\mathrm{POR}_{2,l}$ design.

### 2.3.5 Clear patient-oriented decision

In each informative combination, the physician has only the choice within treatments of the associated mixed pair for the respective patient. For this reason, it is possible to see the choice of the physician directly, if we assume that he did not choose the pair at random.

**Definition 2.3.13 (Clear patient-oriented decision POD).** *The choice of the physician between the two random pairs of one two-pair combination is called a clear patient-oriented decision (*POD*), if the two-pair combination is an informative combination. The set of all informative combinations is defined as* $\mathrm{POD}_{k,l}$.

**Property 2.3.14.** *The number of clear patient-oriented decisions* $|\mathrm{POD}_{k,l}|$ *in a* $\mathrm{POR}_{k,l}$ *design is*

$$|\mathrm{POD}_{k,l}| = \frac{kl(l+k-2)}{2}.$$

*Proof.* From Section 2.3.3, we know that here are $k$ different identical $\mathcal{A}$-pairs with $l(l-1)/2$ pre-images for each $\mathcal{A}$-pair and $l$ different identical $\mathcal{B}$-pairs with $k(k-1)/2$ pre-images in $\mathcal{TPC}_{k,l}$. We also know that no informative combination with two identical pairs exists, otherwise we would have selected two identical pairs from the set of possible pairs. Hence the number of clear patient-oriented decisions can be calculated from (2.1) and (2.2) as

$$\left|\Psi_{\mathcal{A}}^{-1}([A_i,A_i])\right| \cdot k + \left|\Psi_{\mathcal{B}}^{-1}([B_j,B_j])\right| \cdot l = \frac{l(l-1)}{2} \cdot k + \frac{k(k-1)}{2} \cdot l = \frac{kl(l+k-2)}{2}.$$

□

**Property 2.3.15.** *The probability for a clear patient-oriented decision is equal to*

$$\mathbb{P}\Big(\Psi_{\mathcal{A}}^{-1}\Big(\bigcup_{i=1}^{k}[A_i,A_i]\Big)\Big) + \mathbb{P}\Big(\Psi_{\mathcal{B}}^{-1}\Big(\bigcup_{j=1}^{l}[B_j,B_j]\Big)\Big) = \frac{l+k-2}{kl-1}.$$

*Proof.* Since $[A_i, A_i]$ for $i = 1, \ldots, k$ and $[B_j, B_j]$ for $j = 1, \ldots, l$ are disjoint, we have

$$\begin{aligned}
\mathbb{P}\Big(\Psi_{\mathcal{A}}^{-1}\Big(\bigcup_{i=1}^{k}[A_i, A_i]\Big)\Big) + \mathbb{P}\Big(\Psi_{\mathcal{B}}^{-1}\Big(\bigcup_{j=1}^{l}[B_j, B_j]\Big)\Big) &= \sum_{i=1}^{k}\mathbb{P}\big(\Psi_{\mathcal{A}}^{-1}([A_i, A_i])\big) + \sum_{j=1}^{l}\mathbb{P}\big(\Psi_{\mathcal{B}}^{-1}([B_j, B_j])\big) \\
&= \sum_{i=1}^{k}\frac{\left|\Psi_{\mathcal{A}}^{-1}([A_i, A_i])\right|}{|\mathcal{TPC}_{k,l}|} + \sum_{j=1}^{l}\frac{\left|\Psi_{\mathcal{B}}^{-1}([B_j, B_j])\right|}{|\mathcal{TPC}_{k,l}|} \\
&\overset{(2.1)(2.2)}{=} \sum_{i=1}^{k}\frac{l-1}{k(kl-1)} + \sum_{j=1}^{l}\frac{k-1}{l(kl-1)} \\
&= k \cdot \frac{l-1}{k(kl-1)} + l \cdot \frac{k-1}{l(kl-1)} \\
&= \frac{l-1}{kl-1} + \frac{k-1}{kl-1} \\
&= \frac{l+k-2}{kl-1}.
\end{aligned}$$

□

**Remark.** For $k = 1$, the probability for a clear patient-oriented decision is equal to 1.

**Property 2.3.16.** *The sequence*

$$(c_{k,l})_{k\in\mathbb{N}\setminus\{1\}, l\in\mathbb{N}\setminus\{1\}} := \frac{l+k-2}{kl-1},$$

*in $k$ and $l$ describes the probability for a clear patient-oriented decision. For $k = const.$, $(c_{.,l})_{l\in\mathbb{N}\setminus\{1\}}$ is strictly monotonically decreasing and convergent to $1/k$. For $l = const.$, the sequence $(c_{k,.})_{k\in\mathbb{N}\setminus\{1\}}$ is strictly monotonically decreasing and convergent to $1/l$.*

*Proof.* The denominators of $(c_{.,l})_{l\in\mathbb{N}\setminus\{1\}}$ and $(c_{k,.})_{k\in\mathbb{N}\setminus\{1\}}$ are affine linear in $k$ respectively in $l$. Let $k = const.$, then the sequence $(c_{.,l})_{l\in\mathbb{N}\setminus\{1\}}$ can be obtained from $(a_n)_{n\in\mathbb{N}\setminus\{1\}}$ of Lemma 2.3.9 with $n = l$, $\alpha = 1$, $\beta = k-2$, $\gamma = 0$, $\delta = k$ and $\varepsilon = -1$. Hence the sequence is convergent to $\alpha/\delta = \alpha/\delta = 1/k$. To show the monotonicity, we only have to prove condition $\beta\delta > \alpha\varepsilon$. To this end consider

$$\beta\delta > \alpha\varepsilon \quad \Leftrightarrow \quad (k-2)k > -1 \quad \Leftrightarrow \quad (k-1)^2 > 0,$$

which is true.

Let $l = const.$, then the results are obtained by symmetry, by simply interchanging of $k$ and $l$ in $(c_{k,l})_{k\in\mathbb{N}\setminus\{1\}, l\in\mathbb{N}\setminus\{1\}}$, because

$$(c_{l,k})_{k\in\mathbb{N}\setminus\{1\}, l\in\mathbb{N}\setminus\{1\}} = \frac{k+l-2}{lk-1} = (c_{k,l})_{k\in\mathbb{N}\setminus\{1\}, l\in\mathbb{N}\setminus\{1\}}.$$

□

**Example.**

- In Table 2.2 and Figure 2.8, the probabilities of clear patient-oriented decisions for different numbers of treatments $k$ and $l$ are presented.
- For a $\mathrm{POR}_{2,2}$ design, the number of clear patient-oriented decisions is $|\mathrm{POD}_{2,2}| = 4$. Since the number of two-pair combinations is 6, we obtain a probability of 2/3 for clear patient-oriented decisions.

| $k\backslash l$ | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| 2 | 0.67 | 0.60 | 0.57 | 0.56 | 0.55 | 0.54 | 0.53 | 0.53 | 0.53 |
| 3 | | 0.50 | 0.45 | 0.43 | 0.41 | 0.40 | 0.39 | 0.38 | 0.38 |
| 4 | | | 0.40 | 0.37 | 0.35 | 0.33 | 0.32 | 0.31 | 0.31 |
| 5 | | | | 0.33 | 0.31 | 0.29 | 0.28 | 0.27 | 0.27 |
| 6 | | | | | 0.29 | 0.27 | 0.26 | 0.25 | 0.24 |
| 7 | | | | | | 0.25 | 0.24 | 0.23 | 0.22 |
| 8 | | | | | | | 0.22 | 0.21 | 0.20 |
| 9 | | | | | | | | 0.20 | 0.19 |
| 10 | | | | | | | | | 0.18 |

Table 2.2: Probability for a clear patient-oriented decision depending on the numbers of treatments $k$ in strategy $\mathcal{A}$ and $l$ in strategy $\mathcal{B}$.

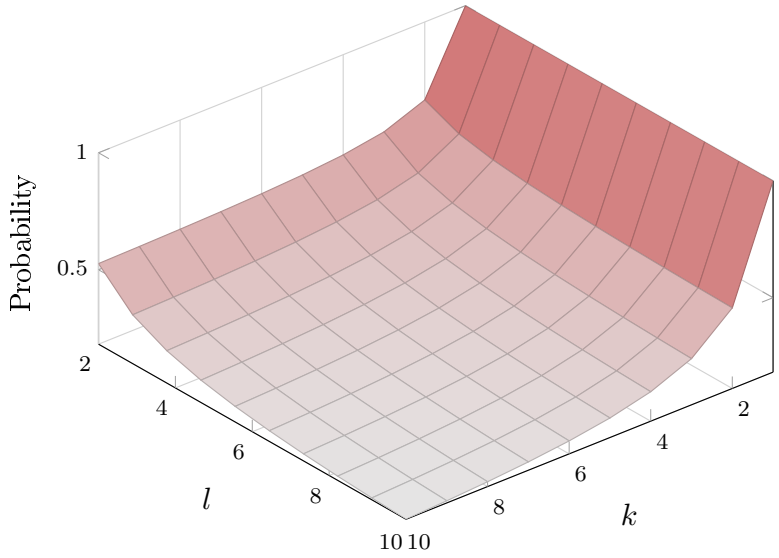



Figure 2.8: Probability for clear patient-oriented decision in a $\mathrm{POR}_{k,l}$ design.

### 2.3.6 Exampels the $\mathrm{POR}_{2,3}$, $\mathrm{POR}_{3,3}$ and $\mathrm{POR}_{2,4}$ design

**Example.** As we have seen in Section 2.3.2, the number of two-pair combinations increases quadratically with the number of pairs. Hence certain values of $k, l$ are practicable only for large sample sizes. Therefore, in addition to the presented example $\mathrm{POR}_{2,2}$ design, the designs $\mathrm{POR}_{2,3}$, $\mathrm{POR}_{2,4}$ and $\mathrm{POR}_{3,3}$ are of practical interest. Table 2.3 summarises the theoretical properties of these designs.

| $\mathrm{POR}_{k,l}$ | Pairs | $\lvert\mathcal{TPC}_{k,l}\rvert$ | $\lvert\mathrm{POD}_{k,l}\rvert$ | $p_{\mathcal{A}}$ | $q_{\mathcal{A}}$ | $p_{\mathcal{B}}$ | $q_{\mathcal{B}}$ | $\mathrm{POD}_{kl}$ |
|---|---|---|---|---|---|---|---|---|
| $\mathrm{POR}_{2,2}$ | 4 | 6 | 4 | 1/6 | 2/3 | 1/6 | 2/3 | 2/3 |
| $\mathrm{POR}_{2,3}$ | 6 | 15 | 9 | 1/5 | 3/5 | 1/15 | 4/15 | 3/5 |
| $\mathrm{POR}_{2,4}$ | 8 | 28 | 16 | 3/14 | 4/7 | 1/28 | 1/7 | 4/7 |
| $\mathrm{POR}_{3,3}$ | 9 | 36 | 18 | 1/12 | 1/4 | 1/12 | 1/4 | 1/2 |

Table 2.3: Theoretical properties of $\mathrm{POR}_{2,2}$, $\mathrm{POR}_{2,3}$, $\mathrm{POR}_{2,4}$ and $\mathrm{POR}_{3,3}$ design.

Tables 2.4–2.6 provide an overview on the patient-oriented decisions within the two-pair combinations. Table 2.4 illustrates the NeSSy design. In 9 out of the 15 two-pair combinations, the physician has a clear choice between two treatments of one strategy. In the first three lines, there is a clear choice in the $\mathcal{A}$ strategy between $A_1$ and $A_2$ (20% of all two-pair combinations). In the $\mathcal{B}$ strategy, there are three kinds of clear treatment decision: $[B_1, B_2]$, $[B_1, B_3]$ and $[B_2, B_3]$. For each of these pairs, there are two two-pair combinations (13.3% of all two-pair combinations) with a patient-oriented decision.

| Number of two-pair combination | $\mathcal{TPC}_{2,3}$ | | Equivalence class in | |
|---|---|---|---|---|
| | Random pair 1 | Random pair 2 | $A \underset{2,3}{\otimes} \mathcal{A}$ | $\mathcal{B} \underset{2,3}{\otimes} \mathcal{B}$ |
| Clear decision between $A_1 \leftrightarrow A_2$ | | | | |
| 1 | $(A_1, B_1)$ | $(A_2, B_1)$ | $[A_1, A_2]$ | $[B_1, B_1]$ |
| 2 | $(A_1, B_2)$ | $(A_2, B_2)$ | $[A_1, A_2]$ | $[B_2, B_2]$ |
| 3 | $(A_1, B_3)$ | $(A_2, B_3)$ | $[A_1, A_2]$ | $[B_3, B_3]$ |
| Clear decision between $B_1 \leftrightarrow B_2$ | | | | |
| 4 | $(A_1, B_1)$ | $(A_1, B_2)$ | $[A_1, A_1]$ | $[B_1, B_2]$ |
| 5 | $(A_2, B_1)$ | $(A_2, B_2)$ | $[A_2, A_2]$ | $[B_1, B_2]$ |
| Clear decision between $B_1 \leftrightarrow B_3$ | | | | |
| 6 | $(A_1, B_1)$ | $(A_1, B_3)$ | $[A_1, A_1]$ | $[B_1, B_3]$ |
| 7 | $(A_2, B_1)$ | $(A_2, B_3)$ | $[A_2, A_2]$ | $[B_1, B_3]$ |
| Clear decision between $B_2 \leftrightarrow B_3$ | | | | |
| 8 | $(A_1, B_2)$ | $(A_1, B_3)$ | $[A_1, A_1]$ | $[B_2, B_3]$ |
| 9 | $(A_2, B_2)$ | $(A_2, B_3)$ | $[A_2, A_2]$ | $[B_2, B_3]$ |
| Non clear decision | | | | |
| 10 | $(A_1, B_1)$ | $(A_2, B_2)$ | $[A_1, A_2]$ | $[B_1, B_2]$ |
| 11 | $(A_1, B_1)$ | $(A_2, B_3)$ | $[A_1, A_2]$ | $[B_1, B_3]$ |
| 12 | $(A_1, B_2)$ | $(A_2, B_1)$ | $[A_1, A_2]$ | $[B_2, B_1]$ |
| 13 | $(A_1, B_2)$ | $(A_2, B_3)$ | $[A_1, A_2]$ | $[B_2, B_3]$ |
| 14 | $(A_1, B_3)$ | $(A_2, B_1)$ | $[A_1, A_2]$ | $[B_3, B_1]$ |
| 15 | $(A_1, B_3)$ | $(A_2, B_2)$ | $[A_1, A_2]$ | $[B_3, B_2]$ |

Table 2.4: There are 15 possibilities of two-pair combinations for the $\text{POR}_{2,3}$ design. The identical pairs in strategy $\mathcal{A}$ and strategy $\mathcal{B}$ are highlighted.

| Number of two-pair combination | $\mathcal{TPC}_{2,4}$ | | Equivalence class in | |
|---|---|---|---|---|
| | Random pair 1 | Random pair 2 | $A \underset{2,4}{\otimes} \mathcal{A}$ | $\mathcal{B} \underset{2,4}{\otimes} \mathcal{B}$ |
| | Clear decision between $A_1 \leftrightarrow A_2$ | | | |
| 1 | $(A_1, B_1)$ | $(A_2, B_1)$ | $[A_1, A_2]$ | $[B_1, B_1]$ |
| 2 | $(A_1, B_2)$ | $(A_2, B_2)$ | $[A_1, A_2]$ | $[B_2, B_2]$ |
| 3 | $(A_1, B_3)$ | $(A_2, B_3)$ | $[A_1, A_2]$ | $[B_3, B_3]$ |
| 4 | $(A_1, B_4)$ | $(A_2, B_4)$ | $[A_1, A_2]$ | $[B_4, B_4]$ |
| | Clear decision between $B_1 \leftrightarrow B_2$ | | | |
| 5 | $(A_1, B_1)$ | $(A_1, B_2)$ | $[A_1, A_1]$ | $[B_1, B_2]$ |
| 6 | $(A_2, B_1)$ | $(A_2, B_2)$ | $[A_2, A_2]$ | $[B_1, B_2]$ |
| | Clear decision between $B_1 \leftrightarrow B_3$ | | | |
| 7 | $(A_1, B_1)$ | $(A_1, B_3)$ | $[A_1, A_1]$ | $[B_1, B_3]$ |
| 8 | $(A_2, B_1)$ | $(A_2, B_3)$ | $[A_2, A_2]$ | $[B_1, B_3]$ |
| | Clear decision between $B_1 \leftrightarrow B_4$ | | | |
| 9 | $(A_1, B_1)$ | $(A_1, B_4)$ | $[A_1, A_1]$ | $[B_1, B_4]$ |
| 10 | $(A_2, B_1)$ | $(A_2, B_4)$ | $[A_2, A_2]$ | $[B_1, B_4]$ |
| | Clear decision between $B_2 \leftrightarrow B_3$ | | | |
| 11 | $(A_1, B_2)$ | $(A_1, B_3)$ | $[A_1, A_1]$ | $[B_2, B_3]$ |
| 12 | $(A_2, B_2)$ | $(A_2, B_3)$ | $[A_2, A_2]$ | $[B_2, B_3]$ |
| | Clear decision between $B_2 \leftrightarrow B_4$ | | | |
| 13 | $(A_1, B_2)$ | $(A_1, B_4)$ | $[A_1, A_1]$ | $[B_2, B_4]$ |
| 14 | $(A_2, B_2)$ | $(A_2, B_4)$ | $[A_2, A_2]$ | $[B_2, B_4]$ |
| | Clear decision between $B_3 \leftrightarrow B_4$ | | | |
| 15 | $(A_1, B_3)$ | $(A_1, B_4)$ | $[A_1, A_1]$ | $[B_3, B_4]$ |
| 16 | $(A_2, B_3)$ | $(A_2, B_4)$ | $[A_2, A_2]$ | $[B_3, B_4]$ |
| | Non clear decision | | | |
| 17 | $(A_1, B_1)$ | $(A_2, B_2)$ | $[A_1, A_2]$ | $[B_1, B_2]$ |
| 18 | $(A_1, B_1)$ | $(A_2, B_3)$ | $[A_1, A_2]$ | $[B_1, B_3]$ |
| 19 | $(A_1, B_1)$ | $(A_2, B_4)$ | $[A_1, A_2]$ | $[B_1, B_4]$ |
| 20 | $(A_1, B_2)$ | $(A_2, B_1)$ | $[A_1, A_2]$ | $[B_2, B_1]$ |
| 21 | $(A_1, B_2)$ | $(A_2, B_3)$ | $[A_1, A_2]$ | $[B_2, B_3]$ |
| 22 | $(A_1, B_2)$ | $(A_2, B_4)$ | $[A_1, A_2]$ | $[B_2, B_4]$ |
| 23 | $(A_1, B_3)$ | $(A_2, B_1)$ | $[A_1, A_2]$ | $[B_3, B_1]$ |
| 24 | $(A_1, B_3)$ | $(A_2, B_2)$ | $[A_1, A_2]$ | $[B_3, B_2]$ |
| 25 | $(A_1, B_3)$ | $(A_2, B_4)$ | $[A_1, A_2]$ | $[B_3, B_4]$ |
| 26 | $(A_1, B_4)$ | $(A_2, B_1)$ | $[A_1, A_2]$ | $[B_4, B_1]$ |
| 27 | $(A_1, B_4)$ | $(A_2, B_2)$ | $[A_1, A_2]$ | $[B_4, B_2]$ |
| 28 | $(A_1, B_4)$ | $(A_2, B_3)$ | $[A_1, A_2]$ | $[B_4, B_3]$ |

Table 2.5: There are 28 possibilities of two-pair combinations for the $\mathrm{POR}_{2,4}$ design. The identical pairs in strategy $\mathcal{A}$ and strategy $\mathcal{B}$ are highlighted.

| Number of two-pair combination | $\mathcal{TPC}_{3,3}$ | | Equivalence class in | |
|---|---|---|---|---|
| | Random pair 1 | Random pair 2 | $A \underset{3,3}{\otimes} \mathcal{A}$ | $\mathcal{B} \underset{3,3}{\otimes} \mathcal{B}$ |
| | Clear decision between $A_1 \leftrightarrow A_2$ | | | |
| 1 | $(A_1, B_1)$ | $(A_2, B_1)$ | $[A_1, A_2]$ | $[B_1, B_1]$ |
| 2 | $(A_1, B_2)$ | $(A_2, B_2)$ | $[A_1, A_2]$ | $[B_2, B_2]$ |
| 3 | $(A_1, B_3)$ | $(A_2, B_3)$ | $[A_1, A_2]$ | $[B_3, B_3]$ |
| | Clear decision between $A_1 \leftrightarrow A_3$ | | | |
| 4 | $(A_1, B_1)$ | $(A_3, B_1)$ | $[A_1, A_3]$ | $[B_1, B_1]$ |
| 5 | $(A_1, B_2)$ | $(A_3, B_2)$ | $[A_1, A_3]$ | $[B_2, B_2]$ |
| 6 | $(A_1, B_3)$ | $(A_3, B_3)$ | $[A_1, A_3]$ | $[B_3, B_3]$ |
| | Clear decision between $A_2 \leftrightarrow A_3$ | | | |
| 7 | $(A_2, B_1)$ | $(A_3, B_1)$ | $[A_2, A_3]$ | $[B_1, B_1]$ |
| 8 | $(A_2, B_2)$ | $(A_3, B_2)$ | $[A_2, A_3]$ | $[B_2, B_2]$ |
| 9 | $(A_2, B_3)$ | $(A_3, B_3)$ | $[A_2, A_3]$ | $[B_3, B_3]$ |
| | Clear decision between $B_1 \leftrightarrow B_2$ | | | |
| 10 | $(A_1, B_1)$ | $(A_1, B_2)$ | $[A_1, A_1]$ | $[B_1, B_2]$ |
| 11 | $(A_2, B_1)$ | $(A_2, B_2)$ | $[A_2, A_2]$ | $[B_1, B_2]$ |
| 12 | $(A_3, B_1)$ | $(A_3, B_2)$ | $[A_3, A_3]$ | $[B_1, B_2]$ |
| | Clear decision between $B_1 \leftrightarrow B_3$ | | | |
| 13 | $(A_1, B_1)$ | $(A_1, B_3)$ | $[A_1, A_1]$ | $[B_1, B_3]$ |
| 14 | $(A_2, B_1)$ | $(A_2, B_3)$ | $[A_2, A_2]$ | $[B_1, B_3]$ |
| 15 | $(A_3, B_1)$ | $(A_3, B_3)$ | $[A_3, A_3]$ | $[B_1, B_3]$ |
| | Clear decision between $B_2 \leftrightarrow B_3$ | | | |
| 16 | $(A_1, B_2)$ | $(A_1, B_3)$ | $[A_1, A_1]$ | $[B_2, B_3]$ |
| 17 | $(A_2, B_2)$ | $(A_2, B_3)$ | $[A_2, A_2]$ | $[B_2, B_3]$ |
| 18 | $(A_3, B_2)$ | $(A_3, B_3)$ | $[A_3, A_3]$ | $[B_2, B_3]$ |
| | Non clear decision | | | |
| 19 | $(A_1, B_1)$ | $(A_2, B_2)$ | $[A_1, A_2]$ | $[B_1, B_2]$ |
| 20 | $(A_1, B_1)$ | $(A_2, B_3)$ | $[A_1, A_2]$ | $[B_1, B_3]$ |
| 21 | $(A_1, B_1)$ | $(A_3, B_2)$ | $[A_1, A_3]$ | $[B_1, B_2]$ |
| 22 | $(A_1, B_1)$ | $(A_3, B_3)$ | $[A_1, A_3]$ | $[B_1, B_3]$ |
| 23 | $(A_1, B_2)$ | $(A_2, B_1)$ | $[A_1, A_2]$ | $[B_2, B_1]$ |
| 24 | $(A_1, B_2)$ | $(A_2, B_3)$ | $[A_1, A_2]$ | $[B_2, B_3]$ |
| 25 | $(A_1, B_2)$ | $(A_3, B_1)$ | $[A_1, A_3]$ | $[B_2, B_1]$ |
| 26 | $(A_1, B_2)$ | $(A_3, B_3)$ | $[A_1, A_3]$ | $[B_2, B_3]$ |
| 27 | $(A_1, B_3)$ | $(A_2, B_1)$ | $[A_1, A_2]$ | $[B_3, B_1]$ |
| 28 | $(A_1, B_3)$ | $(A_2, B_2)$ | $[A_1, A_2]$ | $[B_3, B_2]$ |
| 29 | $(A_1, B_3)$ | $(A_3, B_1)$ | $[A_1, A_3]$ | $[B_3, B_1]$ |
| 30 | $(A_1, B_3)$ | $(A_3, B_2)$ | $[A_1, A_3]$ | $[B_3, B_2]$ |
| 31 | $(A_2, B_1)$ | $(A_3, B_2)$ | $[A_2, A_3]$ | $[B_1, B_2]$ |
| 32 | $(A_2, B_1)$ | $(A_3, B_3)$ | $[A_2, A_3]$ | $[B_1, B_3]$ |
| 33 | $(A_2, B_2)$ | $(A_3, B_1)$ | $[A_2, A_3]$ | $[B_2, B_1]$ |
| 34 | $(A_2, B_2)$ | $(A_3, B_3)$ | $[A_2, A_3]$ | $[B_2, B_3]$ |
| 35 | $(A_2, B_3)$ | $(A_3, B_1)$ | $[A_2, A_3]$ | $[B_3, B_1]$ |
| 36 | $(A_2, B_3)$ | $(A_3, B_2)$ | $[A_2, A_3]$ | $[B_3, B_2]$ |

Table 2.6: There are 36 possibilities of two-pair combinations for the $\text{POR}_{3,3}$ design. The identical pairs in strategy $\mathcal{A}$ and strategy $\mathcal{B}$ are highlighted.

CHAPTER 3

# Allocation probability of a specific treatment

## 3.1 Introduction

In the $\mathrm{POR}_{k,l}$ design discussed in this thesis both strategies are assumed to be balanced (see Remark 3 following Definition 2.3.4). However, due to the selection or deselection of one random pair, it can happen that the treatments in each strategy are unbalanced. The question we like to study in this chapter is how the probability of each treatment to be represented in this study is changed by the physician's choice. To this end, we define the concept of allocation probability of a specific treatment.

**Definition 3.1.1 (Allocation probability)**. *The allocation probability for one treatment $C$ is the proportion of patients treated with $C$ of the total number of patients treated in this study.*

In the first sections of this chapter, we analyse the extreme cases of allocation probabilities which may occur when one treatment is avoided or one treatment is selected whenever possible. These extreme cases are defined as minimum allocation probability and maximum allocation probability. Obviously, the allocation probability of one treatment depends on the allocation probabilities of the other treatments: If the allocation probability increases for a treatment of one strategy, the allocation probability decreases in at least one of the remaining treatments of this strategy.

In the introductory section, we claimed that the patient-oriented randomisation design constitutes an intermediate path between a block randomisation and the CUtLASS design, where, compared to the $\mathrm{POR}_{k,l}$ design, the first step of systematic comparison is missing. The minimum allocation probabilities as well as the maximum allocation probabilities differ between these three designs. Therefore, we define in the last part of this section the two different study designs 'Balanced block randomisation design for two different strategies' and the 'CUtLASS design' and compare their allocation probabilities to the allocation probabilities of the patient-oriented randomisation design.

## 3.2 Minimum allocation probability of a specific treatment

The physician's decision can be seen as deselection of a specific treatment. If the physician would be fully free to decide about the treatments in a clinical trial, it might happen that

non-popular treatments or treatments not meeting personal preferences are unfoundedly omitted and thus not represented in the trial. However, an advantage of the $\text{POR}_{k,l}$ design is that any treatment is administered with a minimum allocation probability, regardless of any physician's preferences. Even if a specific treatment is generally deselected (i.e. physicians always pick the random pair where said treatment is not included, if they have the choice) it is not possible to avoid that treatment completely: the identical pairs ensure that in 50% of the outcomes of this pair, the doubled treatment will be the treatment to be applied (due to the second randomisation step) independent of the physician's choice, even if he had preferred to deselect it.

**Example.** For the $\text{POR}_{2,2}$ design, we rearrange Table 2.1 and consider the informative combinations. We study what happens if the physician deselects for example treatment $A_1$

| Number of two-pair combination | $\mathcal{TPC}_{2,2}$ | | Equivalence class in | |
|---|---|---|---|---|
| | Random pair 1 | Random pair 2 | $A \underset{2,2}{\otimes} \mathcal{A}$ | $\mathcal{B} \underset{2,2}{\otimes} \mathcal{B}$ |
| Clear decision between $A_1 \leftrightarrow A_2$ | | | | |
| 2 | $(A_1, B_1)$ | $(A_2, B_1)$ | $[A_1, A_2]$ | $[B_1, B_1]$ |
| 5 | $(A_1, B_2)$ | $(A_2, B_2)$ | $[A_1, A_2]$ | $[B_2, B_2]$ |
| Clear decision between $B_1 \leftrightarrow B_2$ | | | | |
| 1 | $(A_1, B_1)$ | $(A_1, B_2)$ | $[A_1, A_1]$ | $[B_1, B_2]$ |
| 6 | $(A_2, B_1)$ | $(A_2, B_2)$ | $[A_2, A_2]$ | $[B_1, B_2]$ |
| No clear decision | | | | |
| 3 | $(A_1, B_1)$ | $(A_2, B_2)$ | $[A_1, A_2]$ | $[B_1, B_2]$ |
| 4 | $(A_1, B_2)$ | $(A_2, B_1)$ | $[A_1, A_2]$ | $[B_2, B_1]$ |

Table 3.1: Rearranged two-pair combinations of the $\text{POR}_{2,2}$ design. The identical pairs in strategy $\mathcal{A}$ and strategy $\mathcal{B}$ are highlighted.

whenever possible, independent from the specific patient. Given the two-pair combinations 2 to 5 the physician can avoid treatment $A_1$ by choosing random pair 2 (see Table 3.1). In two-pair combination 6, there is no treatment $A_1$ either in random pair 1 or in random pair 2 thus treatment $A_1$ is avoided automatically. The only critical two-pair combination we concentrate on is two-pair combination 1. If the patient receives this two-pair combination, he will get treatment $A_1$ with 50% probability independent of whether the physician has chosen random pair one or two. This is due to the second random step implemented in the $\text{POR}_{k,l}$ design (see Definitions 2.2.1 and 2.3.4). This results in a minimum allocation probability, which consists of the probability for identical $\mathcal{A}$-pairs which is 1/6 and the probability to be randomised into strategy $\mathcal{A}$ ($p_\Psi = 1/2$). Thus, treatment $A_1$ is administered at least with probability 1/12 for each patient in this study. If we were in a study with 120 randomised patients, the minimum expected number of patients with $A_1$ was 10.

**Definition 3.2.1 (Minimum allocation probability).** *Let $\Theta_{\bar{C}}$ be a special case of $\Theta$ which describes the deselection behaviour (deselection of random pairs containing $C$ whenever possible) of the physician against treatment $C$ in the patient-oriented step of randomisation. Then the minimum allocation probability for treatment $C$ is defined as the probability that this treatment occurs, in case that it is deselected by the physician whenever*

*possible, i.e.*

$$\mathbb{P}_{\Psi\circ\Theta_{\bar{C}}}(\{C\}) = \mathbb{P}\left((\Psi\circ\Theta_{\bar{C}})^{-1}(C)\right).$$

**Notation.** To emphasise that treatment $C$ is deselected, we denote the function $\Theta_{\bar{C}}$ with the complement of $C$ as subscript.

**Property 3.2.2.** *The minimum allocation probability for any treatment $A_i \in \mathcal{A}$ is given by*

$$\mathbb{P}\left((\Psi\circ\Theta_{\bar{A}_i})^{-1}(A_i)\right) = \frac{l-1}{2k(kl-1)} \quad \textit{for} \quad i = 1,\ldots,k$$

*where $\Theta_{\bar{A}_i}$ describes the deselection behaviour of the physician against treatment $A_i$. Similarly, the minimum allocation probability for any treatment $B_j \in \mathcal{B}$ is given by*

$$\mathbb{P}\left((\Psi\circ\Theta_{\bar{B}_j})^{-1}(B_j)\right) = \frac{k-1}{2l(kl-1)} \quad \textit{for} \quad j = 1,\ldots,l,$$

*where $\Theta_{\bar{B}_j}$ describes the deselection behaviour of the physician against treatment $B_j$.*

*Proof.* Since the two random steps are independent, we obtain

$$\mathbb{P}\left((\Psi\circ\Theta_{\bar{A}_i})^{-1}(A_i)\ \right) = \quad p_\Psi\ \mathbb{P}\left(\Theta_{\bar{A}_i}^{-1}([A_i,B_j]),\, j=1,\ldots,l\right).$$

Because of the deselection behaviour of $\Theta_{\bar{A}_i}$ we have

$$\begin{aligned}\Theta_{\bar{A}_i}^{-1}\left([A_i,B_j]\right) &= \left\{[(A_i,B_j),(A_i,B_{j'}] \mid 1\le j,\, j'\le l\right\}\\ &= \Psi_{\mathcal{A}}^{-1}\left([A_i,A_i]\right).\end{aligned}$$

Consequently,

$$\mathbb{P}\left(\Theta_{\bar{A}_i}^{-1}([A_i,B_j]),\, j=1,\ldots,l\right) = \mathbb{P}\left(\Psi_{\mathcal{A}}^{-1}([A_i,A_i])\right) = p_{\mathcal{A}}.$$

Hence we have

$$\mathbb{P}\left((\Psi\circ\Theta_{\bar{A}_i})^{-1}(A_i)\ \right) = p_\Psi\cdot p_{\mathcal{A}} \overset{(2.1)}{=} \frac{l-1}{2k(kl-1)}.$$

Analogously, we obtain the result for $B_j$ by using Equation (2.2). □

**Remark.** The minimum allocation probability differs between the strategies if $k$ and $l$ are different. In this case we determine the average minimum allocation probability to receive a particular treatment $C_i$ regardless of the strategy for $\mathrm{POR}_{k,l}$ by the weighted average

$$\begin{aligned}\mathbb{P}\left((\Psi\circ\Theta_{\bar{C}_i})^{-1}(C_i)\right) &= \frac{1}{k+l}\Big(k\cdot\mathbb{P}\big((\Psi\circ\Theta_{\bar{A}_i})^{-1}(A_i)\big) + l\cdot\mathbb{P}\big((\Psi\circ\Theta_{\bar{B}_j})^{-1}(B_j)\big)\Big)\\ &= \frac{1}{k+l}\left(\frac{k(l-1)}{2k(kl-1)} + \frac{l(k-1)}{2l(kl-1)}\right)\\ &= \frac{k+l-2}{2(kl-1)(k+l)}.\end{aligned}$$

**Property 3.2.3.**

1. *For $k = 1$, the minimum allocation probability for the only $\mathcal{A}$-treatment $A_1$ is $\mathbb{P}\big((\Psi \circ \Theta_{\bar{A}_1})^{-1}(A_1)\big) = 1/2$. For $k \neq 1$, we consider the minimum allocation probability for any treatment $A_i$ from strategy $\mathcal{A}$ as a sequence*

$$(a_{k,l})_{k\in\mathbb{N}\setminus\{1\},\, l\in\mathbb{N}\setminus\{1\}} := \frac{l-1}{2k(kl-1)},$$

*in $k$ and $l$. Then, the sequence $(a_{.,l})_{l\in\mathbb{N}\setminus\{1\}}$ is strictly monotonically increasing for $k = const.$ and convergent to $1/k^2$. For $l = const.$, the sequence $(a_{k,.})_{k\in\mathbb{N}\setminus\{1\}}$ is strictly monotonically decreasing and convergent to 0.*

2. *The minimum allocation for any $\mathcal{B}$-treatment $B_j$ is $\mathbb{P}\big((\Psi \circ \Theta_{\bar{B}_j})^{-1}(B_j)\big) = 0$ for $k = 1$. For $k > 1$, we consider the minimum allocation probability for any treatment $B_j$ from strategy $\mathcal{B}$ as a sequence*

$$(b_{k,l})_{k\in\mathbb{N}\setminus\{1\},\, l\in\mathbb{N}\setminus\{1\}} := \frac{k-1}{2l(kl-1)}.$$

*Then, the sequence $(b_{.,l})_{l\in\mathbb{N}\setminus\{1\}}$ is strictly monotonically decreasing for $k = const.$ and convergent to 0. For $l = const.$, the sequence $(b_{k,.})_{k\in\mathbb{N}\setminus\{1\}}$ is strictly monotonically increasing and convergent to $1/l^2$.*

3. *The average minimum allocation probability is given by $\mathbb{P}\big((\Psi \circ \Theta_{\bar{C}_i})^{-1}(C_i)\big) = 1/(2(l+1))$ for $k = 1$. For $k \neq 1$, the sequence*

$$(c_{k,l})_{k\in\mathbb{N}\setminus\{1\},l\in\mathbb{N}\setminus\{1\}} := \frac{k+l-2}{2(kl-1)(k+l)}$$

*describes the average minimum allocation probability. $(c_{.,l})_{l\in\mathbb{N}\setminus\{1\}}$ is monotonically decreasing for $k = const.$ and convergent to 0. For $l = const.$, $(c_{k,.})_{k\in\mathbb{N}\setminus\{1\}}$ is also monotonically decreasing and convergent to 0.*

*Proof.*

1.-2. Since the sequences of the minimum allocation probabilities for $A_i$ and $B_j$ match up to a factor of 1/2 (see Remark 3 to Definition 2.3.4) with the probabilities of the identical pairs, we refer to the proof of Property 2.3.8.

3. The sequence $(c_{k,l})_{k\in\mathbb{N}\setminus\{1\},\, l\in\mathbb{N}\setminus\{1\}}$ is symmetric in $k$ and $l$. Therefore, we only prove the properties for $k = const.$ Consider

$$(c_{.,l})_{l\in\mathbb{N}\setminus\{1\}} = \frac{l+k-2}{2kl^2 + (2k^2-2)l - 2k}.$$

The denominator of the sequence is a quadratic polynomial in $l$ and the sequence can be obtained from $(a_n)_{n\in\mathbb{N}\setminus\{1\}}$ of Lemma 2.3.9 with $n = l$, $\alpha = 1$, $\beta = k-2$, $\gamma = 2k$, $\delta = 2k^2 - 2$ and $\varepsilon = -2k$. With the help of Lemma 2.3.9, we know that the sequence $(c_{.,l})_{l\in\mathbb{N}\setminus\{1\}}$ is monotonically decreasing and convergent to 0 for all $l > \max(-\beta/\alpha, N(\alpha,\beta,\gamma,\delta,\varepsilon))$. The single terms are given by

$$-\frac{\beta}{\alpha} = \frac{2-k}{1} = 2-k \leq 0$$

and

$$\begin{aligned} N(1, k-2, 2k, 2k^2-2, -2k) &= -\frac{1}{2} - k + 2 \\ &\quad + \sqrt{\frac{1}{4} + k^2 - 4k + 4 - \frac{(k-2)(2k^2-2)}{2k} - 1} \\ &= \frac{3}{2} - k + \sqrt{\frac{13}{4} - \frac{2k^3 - 4k^2 - 2k + 4}{2k} + k^2 - 4k} \\ &= \frac{3}{2} - k + \sqrt{\frac{13}{4} - k^2 + 1 + 2k - \frac{2}{k} + k^2 - 4k} \\ &= \frac{3}{2} - k + \sqrt{\frac{17}{4} - 2k - \frac{2}{k}} \leq 1. \end{aligned}$$

For $k > 1$ the discriminant is smaller than zero and $N$ exists only for $k = 1$. Therefore,

$$-\frac{\beta}{\alpha} \leq 0 < l.$$

□

**Remark.** To increase the minimum allocation probability of one treatment in one strategy, the number of treatments in the other strategy should be increased.

## 3.3 Maximum allocation probability of a specific treatment

The physician's decision can also be seen as selection of a specific treatment, which can increase the probability to receive this treatment in the associated strategy.

**Example.** If the physician prefers one specific treatment for a certain patient, for example $A_1$ in the $\mathrm{POR}_{2,2}$ design, he can choose one random pair containing treatment $A_1$ in the majority of cases, i.e. five of the six two-pair combination contain treatment $A_1$ in at least one random pair. In two-pair combination 1 from Table 3.1, there is always the chance that the patient receives treatment $A_1$ in case he is randomised to strategy $\mathcal{A}$. In two-pair combination 2 to 5 the physician can always chose random pair 1 to obtain a chance of 50% for the patient to receive treatment $A_1$. The random pairs of two-pair combination 6 both contain no treatment $A_1$.

To concentrate only on the choice of the physician in strategy $\mathcal{A}$, we consider all classes of $\mathcal{A}$-pairs of the $\mathrm{POR}_{2,2}$ design

$$\mathcal{A} \underset{2,2}{\otimes} \mathcal{A} = \{[A_1, A_1], [A_1, A_2], [A_2, A_2]\}.$$

Assuming that the physician always chooses a random pair with $\mathcal{A}$-treatment $A_1$ when possible, the patient will receive treatment $A_1$ with probability 1/2 (second randomisation step), when the first randomisation step yield a two-pair combination whose $\mathcal{A}$-pair belongs to either $[A_1, A_1]$ or $[A_1, A_2]$. There are five pre-images of these $\mathcal{A}$-pairs, each of which has a probability of 1/6 to be chosen in the first randomisation step. Hence, when the physician is selecting treatment $A_1$ whenever possible, patients will receive this treatment with probability $5/6 \cdot 1/2 = 5/12$. Obviously, this is the maximum value for the allocation

probability of treatment $A_1$. If we were in a study with 120 randomised patients, the maximum expected number of treated patients with $A_1$ would be 50. Within strategy $\mathcal{A}$, the expected proportion of patients with treatment $A_1$ would be 5/6.

**Definition 3.3.1 (Maximum allocation probability)**. *Let $\Theta_C$ be a special case of $\Theta$ which describes the distribution of the selection behaviour of the physician for treatment $C$ in the patient-oriented step of randomisation with*

$$\Theta_C : (\mathcal{TPC}_{k,l},\, \mathcal{P}(\mathcal{TPC}_{k,l})) \longrightarrow (\mathcal{A} \times \mathcal{B},\, \mathcal{P}(\mathcal{A} \times \mathcal{B})).$$

*Then the maximum allocation probability for treatment $C$ is defined as the probability that this treatment occurs, when it is selected by the physician whenever possible i.e.*

$$\mathbb{P}_{\Psi \circ \Theta_C}(\{C\}) = \mathbb{P}\left((\Psi \circ \Theta_C)^{-1}(C)\right).$$

**Property 3.3.2.** *The maximum allocation probability for any treatment $A_i \in \mathcal{A}$ is given by*

$$\mathbb{P}\left((\Psi \circ \Theta_{A_i})^{-1}(A_i)\right) = \frac{2kl - l - 1}{2k(kl-1)} \quad \textit{for} \quad i = 1, \ldots, k.$$

*Analogously, the maximum allocation probability for any treatment $B_j \in \mathcal{B}$ is given by*

$$\mathbb{P}\left((\Psi \circ \Theta_{B_j})^{-1}(B_j)\right) = \frac{2kl - k - 1}{2l(kl-1)} \quad \textit{for} \quad j = 1, \ldots, l.$$

*Proof.* Because the two randomisation steps are independent, we obtain

$$\mathbb{P}\left((\Psi \circ \Theta_{A_i})^{-1}(A_i)\ \right) = \quad p_\Psi\ \mathbb{P}\left(\Theta_{A_i}^{-1}([A_i,B_j]),\, j = 1, \ldots, l\right). \tag{3.1}$$

Because of the selection behaviour of $\Theta_{A_i}$ we have

$$\begin{aligned}\Theta_{A_i}^{-1}\left([A_i,B_j]\right) &= \left\{[(A_i,B_j),(A_{i'},B_{j'})] \mid 1 \le i' \le k;\ 1 \le j,j' \le l;\ i \ne i' \wedge j \ne j'\right\} \\ &= \Psi_{\mathcal{A}}^{-1}\left([A_i,A_i] \cup \bigcup_{\substack{j=1 \\ j \ne i}}^{k} [A_i,A_j]\right).\end{aligned}$$

Consequently,

$$\begin{aligned}\mathbb{P}\left(\Theta_{A_i}^{-1}([A_i,B_j]),\, j = 1, \ldots, l\right) &= \Psi_{\mathcal{A}}^{-1}\left([A_i,A_i] \cup \bigcup_{\substack{j=1 \\ j \ne i}}^{k} [A_i,A_j]\right) \\ &= \Psi_{\mathcal{A}}^{-1}\left([A_i,A_i]\right) + \Psi_{\mathcal{A}}^{-1}\left(\bigcup_{\substack{j=1 \\ j \ne i}}^{k} [A_i,A_j]\right) \\ &= p_{\mathcal{A}} + (k-1)q_{\mathcal{A}}. \end{aligned} \tag{3.2}$$

Combining Equations (3.1) and (3.2) we obtain

$$\mathbb{P}\left((\Psi \circ \Theta_{A_i})^{-1}(A_i)\right) \quad = \quad p_\Psi \cdot (p_{\mathcal{A}} + (k-1)q_{\mathcal{A}})$$

$$\begin{aligned} &\overset{(2.1)(2.7)}{=} \frac{1}{2}\left(\frac{(l-1)}{k(kl-1)} + (k-1)\frac{2l}{k(kl-1)}\right) \\ &= \frac{l-1+2l(k-1)}{2k(kl-1)} \\ &= \frac{2lk-l-1}{2k(kl-1)}. \end{aligned}$$

Analogously, we obtain the result for $B_j$ with Equations (2.2) and (2.8). □

**Remark.** The maximum allocation probability for a specific treatment is equal for each treatment within each strategy. However, the probability differs in both strategies if $k$ and $l$ are different. In this case, we define the average maximum allocation probability to receive a particular treatment $C_i$ of any strategy for $\mathrm{POR}_{k,l}$ by the weighted averages.

$$\begin{aligned} \mathbb{P}\left((\Psi \circ \Theta_{C_i})^{-1}(C_i)\right) &= \frac{1}{k+l}\Big(k \cdot \mathbb{P}\left((\Psi \circ \Theta_{A_i})^{-1}(A_i)\right) + l \cdot \mathbb{P}\left((\Psi \circ \Theta_{B_i})^{-1}(B_i)\right)\Big) \\ &= \frac{1}{k+l}\left(\frac{k(2lk-l-1)}{2k(kl-1)} + \frac{l(2kl-k-1)}{2l(kl-1)}\right) \\ &= \frac{4kl-l-k-2}{2(kl-1)(k+l)}. \end{aligned}$$

**Property 3.3.3.**

1. *For $k = 1$, the maximum allocation probability for the only $\mathcal{A}$-treatment $A_1$ is equal to $\mathbb{P}\left((\Psi \circ \Theta_{A_1})^{-1}(A_1)\right) = 1/2$. For $k \neq 1$, we consider the maximum allocation probability for $A_i$ as a sequence*

$$(a_{k,l})_{k\in\mathbb{N}\setminus\{1\},\, l\in\mathbb{N}\setminus\{1\}} := \frac{2kl-l-1}{2k(kl-1)},$$

*in $k$ and $l$. The sequence $(a_{.,l})_{l\in\mathbb{N}\setminus\{1\}}$ is strictly monotonically decreasing for $k = const.$ and convergent to $(2k-1)/(2k^2)$. For $l = const.$, the sequence $(a_{k,.})_{k\in\mathbb{N}\setminus\{1\}}$ is monotonically decreasing and convergent to 0.*

2. *For $k = 1$, the maximum allocation probability for the treatment $B_j$ is equal to $\mathbb{P}\left((\Psi \circ \Theta_{B_j})^{-1}(B_j)\right) = 1/l$. Let the maximum allocation probability for $B_j$ considered as a sequence*

$$(b_{k,l})_{k\in\mathbb{N}\setminus\{1\},\, l\in\mathbb{N}\setminus\{1\}} := \frac{2kl-k-1}{2l(kl-1)}$$

*for $k \neq 1$. Then, the sequence $(b_{.,l})_{l\in\mathbb{N}\setminus\{1\}}$ is strictly monotonically decreasing for $k = const.$ and convergent to 0. For $l = const.$, the sequence $(b_{k,.})_{k\in\mathbb{N}\setminus\{1\}}$ is strictly monotonically decreasing and convergent to $(2l-1)/(2l^2)$.*

3. *For $k = 1$, the average maximum allocation probability for a particular treatment $C_i$ of any strategy is equal to $\mathbb{P}\left((\Psi \circ \Theta_{C_i})^{-1}(C_i)\right) = 1/(2(l+1))$. For $k \neq 1$, the sequence*

$$(c_{k,l})_{k\in\mathbb{N}\setminus\{1\},\, l\in\mathbb{N}\setminus\{1\}} := \frac{4kl-l-k-2}{2(kl-1)(k+l)}$$

*describes the average maximum allocation probability.* $(c_{.,l})_{l\in\mathbb{N}\setminus\{1\}}$ *is strictly monotonically decreasing and convergent to* 0 *for* $k = const.$ *and for all* $l > l_0 \geq 2$ *with*

$$l_0 = \max\left(\frac{k+2}{4k-1}, \frac{-2k+5}{2(4k-1)} + \sqrt{-\frac{3}{4} - \frac{4k^4+8k^3-2k^2-3k+2}{k(4k-1)^2}}\right).$$

*For* $l = const.$, $(c_{k,.})_{k\in\mathbb{N}\setminus\{1\}}$ *is strictly monotonically decreasing and convergent to* 0 *and for all* $k > k_0 \geq 2$ *with*

$$k_0 = \max\left(\frac{l+2}{4l-1}, \frac{-2l+5}{2(4l-1)} + \sqrt{-\frac{3}{4} - \frac{4l^4+8l^3-2l^2-3l+2}{l(4l-1)^2}}\right).$$

*Proof.*

1. For $k = const.$, the denominator of the sequence

$$(a_{.,l})_{l\in\mathbb{N}\setminus\{1\}} = \frac{(2k-1)l-1}{2k^2l-2k}$$

is affine linear in $l$. The sequence can be obtained from $(a_n)_{n\in\mathbb{N}\setminus\{1\}}$ of Lemma 2.3.9 with $n = l$, $\alpha = 2k-1$, $\beta = -1$, $\gamma = 0$, $\delta = 2k^2$ and $\varepsilon = -2k$. With Lemma 2.3.9, we know that $(a_{.,l})_{l\in\mathbb{N}\setminus\{1\}}$ is convergent to $\alpha/\delta = (2k-1)/2k^2$. For the monotonicity we investigate the relationship of $\beta\delta = -2k^2$ and $\alpha\varepsilon = (2k-1)(-2k)$

$$\beta\delta > \alpha\varepsilon \quad \Leftrightarrow \quad -2k^2 > -4k^2+2k \quad \Leftrightarrow \quad k^2 > k.$$

Hence, $(a_{.,l})_{l\in\mathbb{N}\setminus\{1\}}$ in strictly monotonically decreasing by Lemma 2.3.9.

For $l = const.$, the sequence

$$(a_{k,.})_{l\in\mathbb{N}\setminus\{1\}} = \frac{2lk-l-1}{2lk^2-2k}$$

can be obtained from $(a_n)_{n\in\mathbb{N}\setminus\{1\}}$ of Lemma 2.3.9 with $n = k$, $\alpha = 2l$, $\beta = -l-1$, $\gamma = 2l$, $\delta = -2$ and $\varepsilon = 0$ and the denominator of this sequence is a quadratic polynomial in $k$. With the help of Lemma 2.3.9, we know that the sequence $(a_{k,.})_{l\in\mathbb{N}\setminus\{1\}}$ is strictly monotonically decreasing for all $k > \max(-\beta/\alpha, N(\alpha,\beta,\gamma,\delta,\varepsilon))$ and convergent. We have

$$-\frac{\beta}{\alpha} = -\frac{-l-1}{2l} = \frac{1}{2} + \frac{1}{2l} \leq 1$$

and

$$\begin{aligned} N(2l, -l-1, 2l, -2, 0) &= -\frac{1}{2} + \frac{1}{2} + \frac{1}{2l} + \sqrt{\frac{1}{4} + \frac{l^2+2l+1}{4l^2} - \frac{-2(-l-1)}{4l^2}} \\ &= \frac{1}{2l} + \sqrt{\frac{2l^2-1}{4l^2}} \leq 1. \end{aligned}$$

From this follows

$$\max\left(-\frac{\beta}{\alpha}, N(\alpha,\,\beta,\,\gamma,\delta,\varepsilon)\right) = \max\left(\frac{1}{2}+\frac{1}{2l}, \frac{1}{2l}+\sqrt{\frac{2l^2-1}{4l^2}}\right) \leq 1 < k.$$

Hence, the sequence is strictly monotonically decreasing for all $k \in \mathbb{N}\setminus\{1\}$ and convergent to 0.

2. The result follows from 1. by symmetry:

$$(a_{k,l})_{k\in\mathbb{N}\setminus\{1\},\, l\in\mathbb{N}\setminus\{1\}} = \frac{2kl-l-1}{2k(lk-1)} = (b_{l,k})_{l\in\mathbb{N}\setminus\{1\},k\in\mathbb{N}\setminus\{1\}}\,.$$

3. The sequence $(c_{k,l})_{k\in\mathbb{N}\setminus\{1\},\, l\in\mathbb{N}\setminus\{1\}}$ is symmetric in $k$ and $l$. Hence, we need to prove the properties only for $k = const.$ Consider

$$(c_{.,l})_{l\in\mathbb{N}\setminus\{1\}} = \frac{(4k-1)l-k-2}{2kl^2+(2k^2-2)l-2k}.$$

The denominator of the sequence is a quadratic polynomial in $l$ and the sequence can be obtained from $(a_n)_{n\in\mathbb{N}\setminus\{1\}}$ of Lemma 2.3.9 with $n=l$, $\alpha = 4k-1$, $\beta = -k-2$, $\gamma = 2k$, $\delta = 2k^2-2$ and $\varepsilon = -2k$. With Lemma 2.3.9, we know that the sequences $(c_{.,l})_{l\in\mathbb{N}\setminus\{1\}}$ is strictly monotonically decreasing for all $l > l_0 := \max(-\beta/\alpha, N(\alpha,\beta,\,\gamma,\delta,\varepsilon))$ and convergent. We have

$$-\frac{\beta}{\alpha} = \frac{k+2}{4k-1} \leq 1$$

as well as

$$\begin{aligned}
N(4k-1,\,-k-2,2k,2k^2-2,\,-2k) &= -\frac{1}{2}-\frac{-k-2}{4k-1} \\
&\quad + \sqrt{\frac{1}{4}+\frac{k^2+4k+4}{(4k-1)^2}+\frac{(k+2)(2k^2-2)}{2k(4k-1)}-1} \\
&= \frac{-4k+1+2k+4}{2(4k-1)} \\
&\quad + \sqrt{-\frac{3}{4}-\frac{4k^4+8k^3-2k^2-3k+2}{k(4k-1)^2}} \\
&= \frac{-2k+5}{2(4k-1)} \\
&\quad + \sqrt{-\frac{3}{4}-\frac{4k^4+8k^3-2k^2-3k+2}{k(4k-1)^2}}.
\end{aligned}$$

For

$$\begin{aligned}
l > l_0 &= \max\left(-\frac{\beta}{\alpha},\, N(\alpha,\beta,\,\gamma,\delta,\varepsilon)\right) \\
&= \max\left(\frac{k+2}{4k-1}, \frac{-2k+5}{2(4k-1)}+\sqrt{-\frac{3}{4}-\frac{4k^4+8k^3-2k^2-3k+2}{k(4k-1)^2}}\right),
\end{aligned}$$

the sequence $(c_{\cdot,l})_{l\in\mathbb{N}\setminus\{1\}}$ is strictly monotonically decreasing and convergent to 0. □

**Example.** At the end of each study, all physicians' decisions lead to a certain allocation ratio for each treatment. Here, the bounds of this allocation probabilities are given by the minimum and the maximum probability allocations. For example, Table 3.2 lists the minimum and the maximum allocation probabilities to receive a specific treatment and the corresponding average allocation probabilities for the patient-oriented randomisation designs $\mathrm{POR}_{2,2}$, $\mathrm{POR}_{2,3}$, $\mathrm{POR}_{2,4}$ and $\mathrm{POR}_{3,3}$.

| $\mathrm{POR}_{k,l}$ | Allocation probability of | | | | | |
|---|---|---|---|---|---|---|
| | $A_i$ | | $B_i$ | | $C_i$ | |
| | min | max | min | max | min | max |
| $\mathrm{POR}_{2,2}$ | 0.08 | 0.42 | 0.08 | 0.42 | 0.08 | 0.42 |
| $\mathrm{POR}_{2,3}$ | 0.10 | 0.40 | 0.03 | 0.30 | 0.06 | 0.34 |
| $\mathrm{POR}_{2,4}$ | 0.11 | 0.39 | 0.02 | 0.23 | 0.05 | 0.29 |
| $\mathrm{POR}_{3,3}$ | 0.04 | 0.29 | 0.04 | 0.29 | 0.04 | 0.29 |

Table 3.2: The minimum and maximum allocation probability for a specific treatment in strategy $\mathcal{A}$, $\mathcal{B}$ and the corresponding average minimum and average maximum allocation probabilities for the patient-oriented randomisation designs $\mathrm{POR}_{2,2}$, $\mathrm{POR}_{2,3}$, $\mathrm{POR}_{2,4}$ and $\mathrm{POR}_{3,3}$.

In the NeSSy design $\mathrm{POR}_{2,3}$, the maximum and the minimum allocation probabilities are different for the treatments of strategy $\mathcal{A}$ and $\mathcal{B}$. In the study, neither the maximum nor the minimum allocation probabilities were reached for one treatment, so that no treatment was totally selected or deselected. The allocation probabilities of the $\mathcal{A}$-treatments amount 18% and 28% and of the $\mathcal{B}$-treatments amount 17%, 25% and 21%.

**Remark.** For $k \neq 1$, only one treatment in one strategy can achieve the maximum allocation probability, respectively the minimum allocation probability. Simultaneously, the minimum and the maximum allocation probability can be achieved only in one strategy. For $k = 2$ or $l = 2$, the following relation applies: If one treatment has the maximum allocation probability, the remaining treatment in this strategy has the minimum allocation probability. Furthermore, if a treatment of one strategy reaches one of the allocation probability bounds, the treatments in the other strategy achieve neither the maximum nor the minimum allocation probability.

In order to assess the maximum and the minimum allocation probability of the $\mathrm{POR}_{k,l}$ design, we will define a kind of block randomisation design in the next section, which also follows the aim of strategy comparison, and compare the allocation probabilities for specific treatments between both designs.

## 3.4 Patient-oriented randomisation design versus balanced block randomisation design

**Definition 3.4.1 (Balanced block randomisation design for two strategies $\mathbf{Block_{k,l}}$).** *Let $\mathcal{A}$ and $\mathcal{B}$ be two strategies with $k$ respectively $l$ treatments. A balanced block randomisation design for two strategies* $\mathrm{Block}_{k,l}$ *is a random allocation of patients which after every $h$ patients (where $h$ is a predefined number called block length), has the following properties:*

1. *The number of assignments is the same for all treatments within each strategy, i.e.* $|A_i| = |A_{i'}|$ *and* $|B_j| = |B_{j'}|$ *for* $i, i' = 1, \ldots, k$ *and* $j, j' = 1, \ldots, l$.

2. *The number of assignments to each strategy is equal, i.e.* $\sum_{i=1}^{k} |A_i| = \sum_{j=1}^{l} |B_j|$.

**Definition 3.4.2 (Minimum block length of a Block$_{k,l}$ design).** *The minimum block length of a balanced block randomisation design for two strategies* $\text{Block}_{k,l}$ *is defined as the smallest number* $h$ *that can be chosen in Definition 3.4.1.*

**Notation.** The minimum block length of a $\text{Block}_{k,l}$ design is denoted by $\text{H}_{k,l}^{\text{Block}}$.

**Example.** To get a feeling for Definitions 3.4.1 and 3.4.2, we consider two balanced block designs $\text{Block}_{2,2}$ and $\text{Block}_{2,3}$. In the first example, we have two treatments in each strategy $\mathcal{A} = \{A_1, A_2\}$ and $\mathcal{B} = \{B_1, B_2\}$. To fulfil the properties from Definition 3.4.1, it is sufficient to take all four treatments at once. The minimum block of $\text{Block}_{2,2}$ consists of

$$A_1 \quad A_2 \quad B_1 \quad \text{and} \quad B_2$$

and the minimum block length $\text{H}_{2,2}^{\text{Block}} = 4$.

In the second example $\text{Block}_{2,3}$, the number of treatments of strategy $\mathcal{B} = \{B_1, B_2, B_3\}$ increases to three. If we take all treatments once like in the first example, we see that property one of Definition 3.4.1 is fulfilled but not the second one. Since we have to maintain the first property, we can only use multiples of the numbers of treatments in each strategy. The least common multiple of two and three is six, so that the minimum block consists of

$$\begin{array}{ccccc} A_1 & A_2 & B_1 & B_2 & B_3 \\ A_1 & A_2 & B_1 & B_2 & B_3 \\ A_1 & A_2 & & & \end{array} .$$

Both strategies are equally often represented and also the treatments are equally often represented within each strategy. The minimum block length $\text{H}_{2,3}^{\text{Block}}$ of $\text{Block}_{2,3}$ is 12. This leads us to the following property.

**Property 3.4.3 (Size of minimum block length of Block$_{k,l}$).** *Let* $\text{LCM}_{k,l}$ *be the least common multiple of* $k$ *and* $l$. *For the minimum block length* $\text{H}_{k,l}^{\text{Block}}$ *of the balanced block randomisation design for two strategies* $\text{Block}_{k,l}$, *we have*

$$\text{H}_{k,l}^{\text{Block}} = 2 \cdot \text{LCM}_{k,l}.$$

*Proof.* From the two properties of Definition 3.4.1 we obtain that

$$\sum_{i=1}^{k} |A_i| = \sum_{j=1}^{l} |B_j| \quad \overset{\text{Prop. 1}}{\Leftrightarrow} \quad \sum_{i=1}^{k} |A_1| = \sum_{j=1}^{l} |B_1| \quad \Leftrightarrow \quad k \cdot |A_1| = l \cdot |B_1|.$$

Hence, $k \cdot |A_1|$ and $l \cdot |B_1|$ are multiples of both $k$ and $l$. Since we are searching for the minimum block length, they should both equal to $\text{LCM}_{k,l}$. Consequently

$$|A_1| = \frac{\text{LCM}_{k,l}}{k}$$

and

$$|B_1| = \frac{\mathrm{LCM}_{k,l}}{l}.$$

Because of Property one of Definition 3.4.1 this also applies to the other treatments in $\mathcal{A}$ and $\mathcal{B}$. The minimum block length is therefore given by

$$\begin{aligned}
\mathrm{H}_{k,l}^{\mathrm{Block}} &= \sum_{i=1}^{k} |A_i| + \sum_{j=1}^{l} |B_j| \\
&= \sum_{i=1}^{k} \frac{\mathrm{LCM}_{k,l}}{k} + \sum_{j=1}^{l} \frac{\mathrm{LCM}_{k,l}}{l} \\
&= k \cdot \frac{\mathrm{LCM}_{k,l}}{k} + l \cdot \frac{\mathrm{LCM}_{k,l}}{l} \\
&= 2 \cdot \mathrm{LCM}_{k,l}.
\end{aligned}$$

□

**Remark.** From this, we can also compute an allocation probability for the appearance of the treatments $A_i$ and $B_j$. Let $\Upsilon$ be a random variable which indicates to which treatment the patient is randomised, then we obtain for the allocation probability for treatment $A_i$

$$\mathbb{P}(\Upsilon = A_i) = \frac{|A_i|}{\mathrm{H}_{k,l}^{\mathrm{Block}}} = \frac{\mathrm{LCM}_{k,l}}{k \cdot 2\mathrm{LCM}_{k,l}} = \frac{1}{2k}$$

and for the allocation probability to receive treatment $B_j$

$$\mathbb{P}(\Upsilon = B_j) = \frac{|B_j|}{\mathrm{H}_{k,l}^{\mathrm{Block}}} = \frac{\mathrm{LCM}_{k,l}}{l \cdot 2\mathrm{LCM}_{k,l}} = \frac{1}{2l}.$$

Since this probabilities are different for strategies with different numbers of treatments, we calculate the average allocation probability to receive treatment $C_i \in \mathcal{A} \cup \mathcal{B}$

$$\begin{aligned}
\mathbb{P}(\Upsilon = C_i) &= \frac{1}{k+l}(k \cdot \mathbb{P}(\Upsilon = A_i) + l \cdot \mathbb{P}(\Upsilon = B_j)) \\
&= \frac{1}{k+l}\left(\frac{k}{2k} + \frac{l}{2l}\right) \\
&= \frac{1}{k+l}.
\end{aligned}$$

**Property 3.4.4.**

1. *The ratio between the average maximum allocation probability of a* $\mathrm{POR}_{k,l}$ *design and the average allocation probability of a* $\mathrm{Block}_{k,l}$ *design to receive a particular treatment* $C_i$ *is*

$$\frac{\mathbb{P}\left((\Psi \circ \Theta_{C_i})^{-1}(C_i)\right)}{\mathbb{P}(\Upsilon = C_i)} = \frac{4kl - l - k - 2}{2(kl-1)} > 1.$$

*If we consider the ratio as a sequence* $(c_{k,l})_{k \in \mathbb{N}\setminus\{1\}, l \in \mathbb{N}\setminus\{1\}}$, *then the sequence* $(c_{\cdot,l})_{l \in \mathbb{N}\setminus\{1\}}$ *is strictly monotonically increasing and convergent to* $(4k-1)/(2k)$ *for*

*$k = const$. The sequence $(c_{k,.})_{l\in\mathbb{N}\setminus\{1\}}$ is strictly monotonically increasing and convergent to $(4l-1)/(2l)$ for $l = const$.*

2. *The ratio between the average minimum allocation probability of a $\mathrm{POR}_{k,l}$ design and the average allocation probability of a $\mathrm{Block}_{k,l}$ design to receive a particular treatment $C_i$ is*

$$\frac{\mathbb{P}\left((\Psi\circ\Theta_{\bar{C}_i})^{-1}(C_i)\right)}{\mathbb{P}(\Upsilon = C_i)} = \frac{k+l-2}{2(kl-1)} < 1.$$

*If we consider the ratio as a sequence $(d_{k,l})_{k\in\mathbb{N}\setminus\{1\},\, l\in\mathbb{N}\setminus\{1\}}$, then the sequence $(d_{.,l})_{l\in\mathbb{N}\setminus\{1\}}$ is strictly monotonically decreasing and convergent to $1/(2k)$ for $k = const$. The sequence $(d_{k,.})_{l\in\mathbb{N}\setminus\{1\}}$ is strictly monotonically decreasing and convergent to $1/(2l)$ for $l = const$.*

*Proof.*

1. We can easily prove the first statement of the inequality

$$\frac{4kl-l-k-2}{2(kl-1)} > 1 \quad\Leftrightarrow\quad 2kl-l-k>0 \quad\Leftrightarrow\quad \underbrace{k(l-1)}_{>0}+\underbrace{l(k-1)}_{\geq 0} > 0.$$

For the other properties, we prove only the case $k = const$, since the sequence $(c_{k,l})_{k\in\mathbb{N}\setminus\{1\},\, l\in\mathbb{N}\setminus\{1\}}$ is symmetric in $k$ and $l$. Consider

$$(c_{.,l})_{l\in\mathbb{N}\setminus\{1\}} = \frac{(4k-1)l-k-2}{2kl-2}.$$

The denominator of the sequence is affine linear in $l$ and the sequence can be obtained from $(a_n)_{n\in\mathbb{N}\setminus\{1\}}$ of Lemma 2.3.9 with $n = l$, $\alpha = 4k-1$, $\beta = -k-2$, $\gamma = 0$, $\delta = 2k$ and $\varepsilon = -2$. With Lemma 2.3.9, we know that $(c_{.,l})_{l\in\mathbb{N}\setminus\{1\}}$ is convergent to $\alpha/\delta = (4k-1)/(2k) = 2-1/(2k)$. For the monotonicity we investigate the relationship of $\beta\delta = -2k^2-4k$ and $\alpha\varepsilon = -8k-2$ and receive

$$\begin{aligned}
\beta\delta < \alpha\varepsilon \quad &\Leftrightarrow \quad -2k^2-4k < -8k+2\\
&\Leftrightarrow \quad 2k^2-4k+2 > 0\\
&\Leftrightarrow \quad k(k-2)+2 > 0, \quad \text{true statment.}
\end{aligned}$$

Hence, $(c_{.,l})_{l\in\mathbb{N}\setminus\{1\}}$ is strictly monotonically increasing.

2. The first statement we can also easily proof by transposing the inequality

$$\frac{k+l-2}{2(kl-1)} < 1 \quad\Leftrightarrow\quad -2kl+l+k<0 \quad\Leftrightarrow\quad 2kl-l-k>0,$$

true statement. See case 1 above. The further claims for the sequence $(d_{k,l})_{k\in\mathbb{N}\setminus\{1\},\, l\in\mathbb{N}\setminus\{1\}}$ are verified only for $k = const.$ due to symmetric reasons. The denominator of the sequence is affine linear in $l$ and the sequence can be obtained from $(a_n)_{n\in\mathbb{N}\setminus\{1\}}$ of Lemma 2.3.9 with $n = l$, $\alpha = 1$, $\beta = k-2$,$\gamma = 0, \delta = 2k$ and $\varepsilon = -2$. With Lemma 2.3.9, we know that $(d_{.,l})_{l\in\mathbb{N}\setminus\{1\}}$ is convergent to $\alpha/\delta = 1/(2k)$. For the monotonicity we investigate the relationship between $\beta\delta = 2k^2-4k$ and $\alpha\varepsilon = -2$

and receive

$$\begin{aligned} \beta\delta > \alpha\varepsilon \quad &\Leftrightarrow \quad 2k^2 - 4k > -2 \\ &\Leftrightarrow \quad k^2 - 2k + 1 > 0 \\ &\Leftrightarrow \quad (k-1)^2 > 0, \quad \text{true statement.} \end{aligned}$$

Hence, $(d_{.,l})_{l \in \mathbb{N}\setminus\{1\}}$ is strictly monotonically decreasing. □

**Conclusion 3.4.5.** *The following inequality applies*

$$\mathbb{P}\left((\Psi \circ \Theta_{\bar{C}_i})^{-1}(C_i)\right) < \mathbb{P}(\Upsilon = C_i) < \mathbb{P}\left((\Psi \circ \Theta_{C_i})^{-1}(C_i)\right).$$

**Remark.**

- For $k = 1$, the ratio of the average maximum allocation probability of a $\mathrm{POR}_{1,\,l}$ design and the average allocation probability of a $\mathrm{Block}_{1,\,l}$ design for treatment $C_i$ is equal to $3/2$ for all number of treatments $l$ in strategy $\mathcal{B}$.
- For $k = 1$, the ratio of the average minimum allocation probability of a $\mathrm{POR}_{1,\,l}$ design and the average allocation probability of a $\mathrm{Block}_{1,\,l}$ design for treatment $C_i$ is equal to $1/2$ for all number of treatments $l$ in strategy $\mathcal{B}$.
- In Figure 3.1, we see that the allocation probability of a treatment can be almost doubled by a patient-oriented randomisation design in some cases compared to a given balanced block randomisation design for two strategies due to the fact that

$$\frac{\mathbb{P}\left((\Psi \circ \Theta_{C_i})^{-1}(C_i)\right)}{\mathbb{P}(\Upsilon = C_i)} = \frac{4kl - l - k - 2}{2(kl-1)} \underset{k,l\to\infty}{\longrightarrow} 2.$$

Furthermore, the following applies

$$\frac{\mathbb{P}\left((\Psi \circ \Theta_{\bar{C}_i})^{-1}(C_i)\right)}{\mathbb{P}(\Upsilon = C_i)} = \frac{k + l - 2}{2(kl-1)} \underset{k,l\to\infty}{\longrightarrow} 0.$$

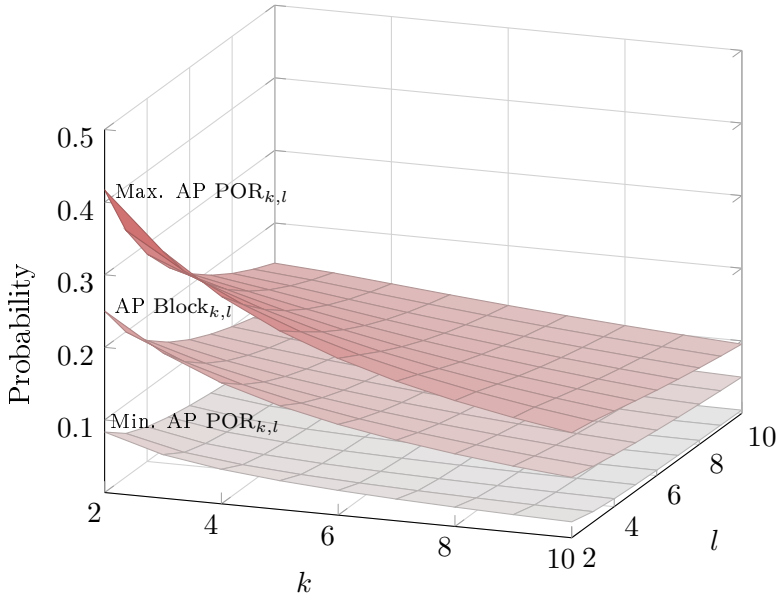



Figure 3.1: Range of the average minimum and the average maximum allocation probability (AP) of a POR$_{k,l}$ design and the average allocation probability of a Block$_{k,l}$ design depending on $k$ and $l$.

## 3.5 Patient-oriented randomisation design versus CUtLASS design

In Section 1.2 'Motivation and background' we introduced the patient-oriented, straightforward RCT design for comparing two strategies in heterogeneous patient collectives implemented in the CUtLASS study (Jones et al., 2006).

**Definition 3.5.1 (CUtLASS design for two strategies).** *Let $\mathcal{A}$ and $\mathcal{B}$ two different strategies with any number of $k$ treatments in strategy $\mathcal{A}$ and $l$ treatments $\mathcal{B}$ with $l \geq \max(2,k)$. Then, the* CUtLASS *design for two strategies* CUtLASS$_{k,l}$ *is defined as a study design which*

- *allows in the first step for physicians a patient-oriented choice for one treatment of each strategy and*
- *randomises in the second step the patient to one strategy $\mathcal{A}$ or $\mathcal{B}$.*

**Notation.**

- Since the random process is the same as the second random process in the POR$_{k,l}$ design, we maintain the definition of our randomisation function $\Psi : (\mathcal{A} \times \mathcal{B}, \mathcal{P}(\mathcal{A} \times \mathcal{B})) \longrightarrow (\mathcal{A} \cup \mathcal{B}, \mathcal{P}(\mathcal{A} \cup \mathcal{B}))$. We also assume here a one-to-one randomisation between strategies as in the POR$_{k,l}$ design ($p_\Psi = 1/2$). Of course in general other $p_\Psi$ are possible if the study goal demands such unequal randomisation.
- We define a new random variable $\Theta^{\text{CUtLASS}}$

$$\Theta^{\text{CUtLASS}} : \left(\mathcal{A}^k \times \mathcal{B}^l, \mathcal{P}(\mathcal{A}^k \times \mathcal{B}^l)\right) \longrightarrow (\mathcal{A} \times \mathcal{B}, \mathcal{P}(\mathcal{A} \times \mathcal{B}))$$

with

$$\mathbb{P}\left((\Theta^{\text{CUtLASS}})^{-1}\left((A_i,B_j)\right)\right) = p_{\Theta}^{ij}$$

for $p_{\Theta}^{ij} \in [0,1]$ which describes the distribution of the patient-oriented step of the physician in CUtLASS design $\text{CUtLASS}_{k,l}$.

- We also define analogous to the $\text{POR}_{k,l}$ design two random variables describing the distribution of the two extreme cases where the physician always deselects or selects one treatment (denoted by $C$ here). That is,

$$\Theta_{\bar{C}}^{\text{CUtLASS}} : \left(\mathcal{A}^k \times \mathcal{B}^l,\, \mathcal{P}(\mathcal{A}^k \times \mathcal{B}^l)\right) \longrightarrow (\mathcal{A} \times \mathcal{B},\, \mathcal{P}(\mathcal{A} \times \mathcal{B}))$$

with

$$\mathbb{P}\left(\left(\Theta_{\bar{C}}^{\text{CUtLASS}}\right)^{-1}\left((A_i,B_j)\right)\right) = \begin{cases} 0 & \text{if } C = A_i \text{ for } j = 1,\ldots,l \\ 0 & \text{if } C = B_j \text{ for } i = 1,\ldots,k \\ p_{\Theta_{\bar{C}}}^{ij} & \text{if } C \neq A_i \text{ and } C \neq B_j \end{cases}$$

describes the distribution of the deselection behaviour of the physician against treatment $C \in \mathcal{A} \cup \mathcal{B}$ and

$$\Theta_{C}^{\text{CUtLASS}} : \left(\mathcal{A}^k \times \mathcal{B}^l,\, \mathcal{P}(\mathcal{A}^k \times \mathcal{B}^l)\right) \longrightarrow (\mathcal{A} \times \mathcal{B},\, \mathcal{P}(\mathcal{A} \times \mathcal{B}))$$

with

$$\mathbb{P}\left((\Theta_{C}^{\text{CUtLASS}})^{-1}((A_i,B_j))\right) = \begin{cases} 0 & \text{if } C \neq A_i \text{ for } j = 1,\ldots,l \\ 0 & \text{if } C \neq B_j \text{ for } i = 1,\ldots,k \\ p_{\Theta_C}^{\cdot j} & \text{if } C = A_i \\ p_{\Theta_C}^{i\cdot} & \text{if } C = B_j \end{cases}$$

describes the selection of a physician who chooses always the treatment $C \in \mathcal{A} \cup \mathcal{B}$.

**Remark.**

- In the CUtLASS design $\text{CUtLASS}_{k,l}$ the physician has $k \cdot l$ different pairs $(A_i, B_j)$, for $i = 1,\ldots,k$ and $j = 1,\ldots,l$, which he can choose from. Since there is no restrictions for the physician's decision, it is possible that some pairs are unrepresented. Consequently, also some treatments may be unrepresented.

- Since the randomisation step and the patient-oriented step are independent in the $\text{CUtLASS}_{k,l}$ design we obtain as the minimum allocation probability for any treatment $A_i \in \mathcal{A}$

$$\begin{aligned} \mathbb{P}\left(\left(\Psi \circ \Theta_{\bar{A}_i}^{\text{CUtLASS}}\right)^{-1}(A_i)\right) &= p_\Psi\, \mathbb{P}\left(\left(\Theta_{\bar{A}_i}^{\text{CUtLASS}}\right)^{-1}\left(\bigcup_{j=1}^{l}(A_i,B_j)\right)\right) \\ &= p_\Psi \cdot 0 \\ &= 0 \qquad \text{for} \quad i = 1,\ldots,k \end{aligned}$$

and analogously as the minimum allocation probability for any treatment $B_j \in \mathcal{B}$

$$\mathbb{P}\left(\left(\Psi \circ \Theta_{B_j}^{\text{CUtLASS}}\right)^{-1}(B_j)\right) = 0 \quad \text{for} \quad j = 1, \ldots, l.$$

- The maximum allocation probability for any treatment $A_i \in \mathcal{A}$ is given by

$$\begin{aligned}\mathbb{P}\left(\left(\Psi \circ \Theta_{A_i}^{\text{CUtLASS}}\right)^{-1}(A_i)\right) =& p_\Psi \, \mathbb{P}\Big(\left(\Theta_{A_i}^{\text{CUtLASS}}\right)^{-1}\Big(\bigcup_{j=1}^{l}(A_i,B_j)\Big)\Big) \\ =& p_\Psi \underbrace{\sum_{j=1}^{l} p_{\Theta_{A_i}}^{\cdot j}}_{=1} \\ =& \frac{1}{2} \quad \text{for} \quad i = 1, \ldots, k,\end{aligned}$$

since all other probabilities for $A_{i'} \neq A_i$ are zero. Analogously, the allocation probability for any treatment $B_j \in \mathcal{B}$ is given by

$$\mathbb{P}\left(\left(\Psi \circ \Theta_{B_j}^{\text{CUtLASS}}\right)^{-1}(B_j)\right) = \frac{1}{2} \quad \text{for} \quad j = 1, \ldots, l.$$

- Since these probabilities are not different for strategies with different numbers of treatments, the average minimum allocation probability for any $C_i \in \mathcal{A} \cup \mathcal{B}$ corresponds to the minimum allocation probability for any treatment $A_i \in \mathcal{A}$ or $\mathcal{B}_j \in \mathcal{B}$. Also the average maximum allocation probability for any $C_i \in \mathcal{A} \cup \mathcal{B}$ corresponds to the maximum allocation probability for any treatment $A_i \in \mathcal{A}$ or $\mathcal{B}_j \in \mathcal{B}$.

  If we add the average minimum and the average maximum allocation probabilities of a CUtLASS$_{k,l}$ design in Figure 3.1, they will be located in the parallel planes limited by the cuboid up- and downwards.

CHAPTER 4

# Balance behaviour and practical implementation

## 4.1 Introduction

In this section, we deal with the practical implementation of the patient-oriented randomisation design. 'Randomisation depends primarily on two interrelated but separate processes, i.e. generation of an unpredictable randomised allocation sequence and concealment of that sequence until assignment occurs (allocation concealment)'(Schulz and Grimes, 2002). We look at how these separate processes are realised in the NeSSy study and we look beyond at possible ways to create the randomisation list to avoid imbalances in strategies $\mathcal{A}$ and $\mathcal{B}$ as well as in the frequencies of two-pair combinations. 'This is important because treatment imbalances may affects statistical power' (Lachin, 1988). We consider the effects in the NeSSy study to discuss possible problems and have a look at models which compute the overall imbalances for different numbers of centres and different types of $\mathrm{POR}_{k,l}$ designs.

## 4.2 Randomisation - applied in the NeSSy study

**Example.** Figure 4.1 illustrates the basic sequence of the randomisation process in one centre as implemented in the NeSSy study. The patients entered the study one by one, and the treatment for each patient had to be known soon after entry. 'The allocation procedure must not be too complex or time-consuming' (White and Freedman, 1978). Therefore, at the beginning of the study the biometric centre created a random list with the complete information about the total process [Z1]. For each random number, the appropriate medication had been centrally packed in two packages [Z4] and sent to the centres together with the information envelope [Z2]. These packages were labelled with the corresponding random number and corresponding encoded information (X and Y) for the first or the second pair choice. When a patient presenting symptoms appeared in the centre, the physician started the screening procedure. If eligible, he informed the patient and asked for consent. After written consent, the patient was admitted and received a random number [1]. The physician reported inclusion of the patient with random number and received [2] an envelope with the information about the two-pair combination for this random number [3]. The physician selected the most suitable pair from this two-pair combination for this patient and justified his choice in the CRF [4]. Afterwards, the

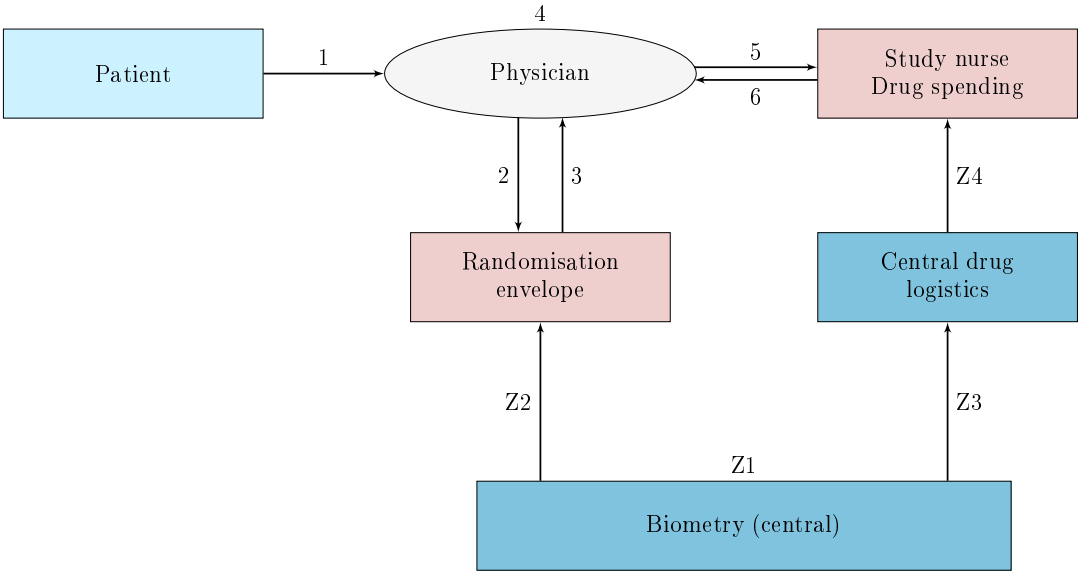



Figure 4.1: Flow chart of the practical implementation of the study design (cf. Schulz et al. (2016a)).

medication administration (study nurse) of the centre was informed about the decision and the random number [5]. On this basis, the physician received the prepared parcel for this random number with the medication provided by the central randomisation [Z3] (double blinded drug $\mathcal{A}$ or drug $\mathcal{B}$ out of the selected pair). He sticked the control label in the CRF and handed over the first drugs for the first weeks contained in the package.

For the control of drug logistics [Z4], a control system had been set up in terms of durability during the whole study period. The demand for medication of patients and centres had been calculated in advance, monitored with special respect to expiry dates, prepared the necessary medication and exchange-planned the return delivery of expired / unused medication from the centres. The specific design caused a greater amount of study drugs to be provided as for each random number two parcels with medication had to be delivered. Medication logistics management tried to recycle the returned unused packages but this procedure was limited especially by expiry dates and rates of recruitment (cf. Schulz et al. (2016a)).

**Example.** In the NeSSy study, blocks were used in preparing randomisation assignments to ensure an equal number of patients in each strategy and of each two-pair combination. The randomisation used a block length of 30 which arised from the number of two-pair combinations and the possibility of randomisation into both strategies ($15 \times 2$). According to the sample size calculations, 630 patients should be recruited into the NeSSy study. For each of the 10 participating centres a randomisation list was created before the trial started, using the method of stratified blocked randomisation in which 'centre' was the prognostic variable (Pocock and Simon, 1975; Lachin, 1988). The randomisation list was completely balanced, i.e. in this list, each of the 15 two-pair combinations was represented 42 times and 315 patients had to be treated with strategy $\mathcal{A}$ and 315 with strategy $\mathcal{B}$. Following internal planning each of the 10 centres should recruit about 60 patients. Thus in the beginning each centre was assigned to two blocks each of length 30.

**Remark.** Following the argumentation in planning the NeSSy study, we assume throughout that patients enter the study one by one, generally over some period of time and the

treatment for each patient will need to be known soon after entry. Therefore, we assume that a total randomisation list is prepared at the beginning of the trial. As there is a risk in some research field that the randomisation list is not fully processed, a block randomisation is used to ensure that there are no large imbalances in the number of patients in each strategy and also in the frequencies of two-pair combinations. 'Further, since a clinic frequently may withdraw (or be dropped) from a study, it is desirable that such withdrawal not affect the validity of the overall randomization plan. For these reasons, it is also generally advocated that randomization in a multicenter trial should be stratified by clinic.' (Lachin, 1988)

**Definition 4.2.1 (Minimum block length of a $\mathrm{POR}_{k,l}$ design).** *Let each entry in the randomisation list be a tuple consisting of one two-pair combination* $\mathrm{TPC}_m$*, for* $m = 1, \ldots, |\mathrm{TPC}|$ *and one strategy, either* $\mathcal{A}$ *or* $\mathcal{B}$*. Then, the minimum block length of a patient-oriented randomisation design* $\mathrm{POR}_{k,l}$ *is defined as smallest block length which fulfils the two following properties:*

1. *Each two-pair combination is randomised with the same frequency for strategy* $\mathcal{A}$ *as for strategy* $\mathcal{B}$*, i.e.*

$$|(\mathrm{TPC}_m, \mathcal{A})| = |(\mathrm{TPC}_m, \mathcal{B})| \quad \textit{for all} \quad m = 1, \ldots, |\mathrm{TPC}|.$$

2. *Each two-pair combination occurs an equal amount of times, i.e.*

$$|(\mathrm{TPC}_m, .)| = |(\mathrm{TPC}_{m'}, .)| \quad \textit{for all} \quad m, m' \in \{1, \ldots, |\mathrm{TPC}|\}.$$

**Notation.** The minimum block length of a $\mathrm{POR}_{k,l}$ design is denoted by $\mathrm{H}_{k,l}^{\mathrm{POR}}$.

**Property 4.2.2 (Size of minimum block length of a $\mathrm{POR}_{k,l}$ design).** *For the minimum block length* $\mathrm{H}_{k,l}^{\mathrm{POR}}$ *of a patient-oriented randomisation design* $\mathrm{POR}_{k,l}$*, we have*

$$\mathrm{H}_{k,l}^{\mathrm{POR}} = 2 \cdot |\mathcal{TPC}_{k,l}| = kl(kl-1).$$

*Proof.* In general, we have

$$\mathrm{H}_{k,l}^{\mathrm{POR}} = \min \sum_{m=1}^{|\mathcal{TPC}_{k,l}|} \left( |(\mathrm{TPC}_m, \mathcal{A})| + |(\mathrm{TPC}_m, \mathcal{B})| \right).$$

From property one of Definition 4.2.1 we know that

$$\mathrm{H}_{k,l}^{\mathrm{POR}} = \min \sum_{m=1}^{|\mathcal{TPC}_{k,l}|} \left( 2 \cdot |(\mathrm{TPC}_m, \mathcal{A})| \right).$$

Property two of Definition 4.2.1 gives that each TPC occurs with the same frequency,

$$\mathrm{H}_{k,l}^{\mathrm{POR}} = \min \left( 2 \cdot |(\mathrm{TPC}_m, \mathcal{A})| \cdot |\mathcal{TPC}_{k,l}| \right).$$

The only parameter we can minimize in this term is $|(\mathrm{TPC}_m, \mathcal{A})|$. Since the block length should be greater than zero, each tuple $|(\mathrm{TPC}_m, \mathcal{A})|$, for $m = 1, \ldots, |\mathrm{TPC}|$, occurs only once and consequently also each tuple $|(\mathrm{TPC}_m, \mathcal{B})|$, for $m = 1, \ldots, |\mathrm{TPC}|$. □

**Example.** The minimum block length of the patient-oriented randomisation designs for the examples of Section 2.3.6 would be 12 for the $\mathrm{POR}_{2,2}$ design, 30 for the $\mathrm{POR}_{2,3}$ design, 56 for the $\mathrm{POR}_{2,4}$ design and 72 for the $\mathrm{POR}_{3,3}$ design. The minimum block length of a patient-oriented randomisation design increases very fast. Also for small numbers of $k$ and $l$, the minimum block length for a patient-oriented randomisation design $\mathrm{H}_{k,l}^{\mathrm{POR}}$ is large.

**Remark.** The minimum number of patients to be recruited should be at least $\mathrm{H}_{k,l}^{\mathrm{POR}}$ to insure that each $\mathrm{TPC}_m$ is randomised in each strategy. Since the minimum block length $\mathrm{H}_{k,l}^{\mathrm{POR}}$ is very large even for small numbers of treatments in each strategy, this is a drawback of a $\mathrm{POR}_{k,l}$ design.

**Example.** During the NeSSy trial, recruiting problems occurred. As a consequence, the large pre-planned sample size of the NeSSy study was reduced to a goal of 150 cases in order to meet the capacities of the centres and the time lines of the study. At the end of the study, 149 patients were randomised. The results of randomisation step 1 (two-pair combinations assigned) are documented in Figure 4.2. As a result of the second step of randomisation 69 (46%) patients were assigned to strategy $\mathcal{A}$ and 80 (54%) patients to strategy $\mathcal{B}$. The participating centres differed in capacities for recruiting patients. Figure 4.3 illustrates the number of patients per centre. Since the pre-planned sample size was

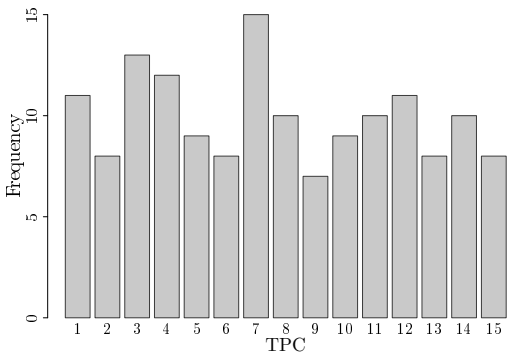



Figure 4.2: Frequencies of two-pair combinations in the NeSSy study.

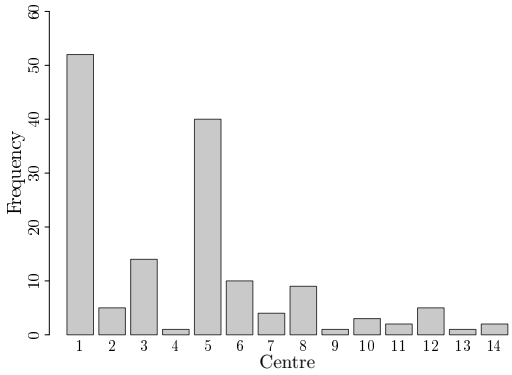



Figure 4.3: Frequencies of patients per centre in the NeSSy study.

not reached, many of the randomisation blocks (each of length 30) were not completely processed due to the large block length and little numbers of recruited patients per centre. Only two centres recruited almost two full blocks with 40% of the patients. Therefore, the observed number of patients per strategy and per two-pair combination differed from the expected numbers. In 149 patients, one would expect that each strategy is covered 74.5 times and every two-pair combination is covered 10 times. However, the observed allocation to strategies was 69 : 80. Although the imbalances are not very large, this shows a disadvantage of the outlined randomisation process.

With the stratified blocked randomisation, there is no imbalance between two-pair combination frequencies, as long as all blocks are filled within each stratum. However, if some or all blocks are not filled as in the NeSSy study, there may occur differences in patient numbers between the strategies or two-pair combination frequencies. In order to assess the problem of imbalance, a mathematical model is built in the next section, which allows us to investigate the relationship between block length, number of strata and the probability distribution of differences in sample sizes between the strategies.

## 4.3 Probability of strategy imbalance

### 4.3.1 Unstratified randomisation

As mentioned in the previous section, we aim to develop a mathematical model which allows us to compute the probability of strategy imbalances. At first, we consider the case where we have only one centre and no stratum otherwise defined. In this case of unstratified randomisation, imbalances in patient numbers between strategies emerge from the fact that one block is not filled completely. Later, we will transfer the idea developed to the stratified blocked randomisation case. The content of this section is based on Kundt (2002). The following proposition can be seen in general with a fixed block length $h$. Especially in the content of the patient-oriented randomisation design, we are mostly interested in the imbalance in blocked randomisation with block length equal to the minimum block length of the $\text{POR}_{k,l}$ design, i.e. $h := \text{H}_{k,l}^{\text{POR}}$. In practice, it could be also possible that a multiple of the minimum block length is used; then $h := b \cdot \text{H}_{k,l}^{\text{POR}}$ with $b \in \mathbb{N}$ (every possible block length is a multiple of the minimum block length).

**Proposition 4.3.1 (Strategy imbalances in blocked randomisation)**. *Assume $N$ patients should be randomised with equal probability to strategy $\mathcal{A}$ and $\mathcal{B}$ in one centre. Let $N_{\mathcal{A}}$ and $N_{\mathcal{B}}$ be the number of patients assigned to strategy $\mathcal{A}$ respectively $\mathcal{B}$ and* $\text{AD} := |D| := |N_{\mathcal{B}} - N_{\mathcal{A}}|$ *be the absolute difference of sample sizes. Then the probability that the absolute difference* AD *for a block randomisation with fixed block length $h$ is at least $e$ is given by*

$$\mathbb{P}(\text{AD} \geq e) = 1 - \frac{2}{h} \sum_{i=1}^{e-1} \sum_{s=0}^{\frac{h}{2}-i} \frac{\binom{\frac{h}{2}}{s}\binom{\frac{h}{2}}{s+i}}{\binom{h}{2s+i}} - \frac{1}{h} \sum_{s=0}^{\frac{h}{2}} \frac{\binom{\frac{h}{2}}{s}\binom{\frac{h}{2}}{s}}{\binom{h}{2s}}.$$

*Proof.* Let $R$ be the number of assignments issued in the last block and $r$ the realisation of $R$, $1 \leq r \leq h$. Furthermore, let $S$ be the number of assignments to strategy $\mathcal{A}$ in the last block and $s$ the realisation of $S$, $1 \leq s \leq h/2$. Then the realisation of the absolute difference $\text{AD} = |N_{\mathcal{B}} - N_{\mathcal{A}}|$ can take values between 0 and $h/2$. Conditional on $R$, $S$ describes the draw of $R$ items from a population of size $h$ that has $h/2$ success states in the population. Hence, $S$ conditional on $R$ is hypergeometric distributed ($S \mid R = r \sim H(h, h/2, r)$). For $R = r$, this implies

$$\mathbb{P}(S = s \mid R = r) = \frac{\binom{\frac{h}{2}}{s}\binom{\frac{h}{2}}{r-s}}{\binom{h}{r}}.$$

Assumed $R$ is uniform over the intergers 1 to $h$, then

$$\mathbb{P}(R = r) = \frac{1}{h}.$$

Next, we calculate separately the probabilities $\mathbb{P}(\text{AD} = 0)$ and $\mathbb{P}(\text{AD} = e)$ for $e \in \mathbb{N}$. This results in

$$\begin{aligned} \mathbb{P}(D = 0) &= \mathbb{P}(R = 2S) \\ &= \sum_{s=0}^{\frac{h}{2}} \mathbb{P}(S = s \mid R = r)\mathbb{P}(R = 2s) \end{aligned}$$

$$= \sum_{s=0}^{\frac{h}{2}} \frac{\binom{\frac{h}{2}}{s}\binom{\frac{h}{2}}{2s-s}}{\binom{h}{2s}} \frac{1}{h}$$
$$= \frac{1}{h} \sum_{s=0}^{\frac{h}{2}} \frac{\binom{\frac{h}{2}}{s}\binom{\frac{h}{2}}{s}}{\binom{h}{2s}}. \tag{4.1}$$

In a similar way, we calculate for $e \in \mathbb{N}$

$$\begin{aligned}
\mathbb{P}(\mathrm{AD} = e) &= \mathbb{P}(D = e \vee D = -e) \\
&= 2\,\mathbb{P}(D = e) \\
&= 2\,\mathbb{P}(R - 2S = e) \\
&= 2 \sum_{s=0}^{\frac{h}{2}-e} \mathbb{P}(S = s, R = 2S + e) \\
&= 2 \sum_{s=0}^{\frac{h}{2}-e} \mathbb{P}(S = s \mid R = 2s + e)\mathbb{P}(R = 2s + e) \\
&= 2 \sum_{s=0}^{\frac{h}{2}-e} \frac{\binom{\frac{h}{2}}{s}\binom{\frac{h}{2}}{2s+e-s}}{\binom{h}{2s+e}} \frac{1}{h} \\
&= \frac{2}{h} \sum_{s=0}^{\frac{h}{2}-e} \frac{\binom{\frac{h}{2}}{s}\binom{\frac{h}{2}}{s+e}}{\binom{h}{2s+e}}.
\end{aligned} \tag{4.2}$$

Combining equations (4.1) and (4.2), we obtain

$$\begin{aligned}
\mathbb{P}(\mathrm{AD} \geq e) &= 1 - \mathbb{P}(\mathrm{AD} < e) \\
&= 1 - \sum_{i=0}^{e-1} \mathbb{P}(\mathrm{AD} = i) \\
&= 1 - \sum_{i=1}^{e-1} \mathbb{P}(\mathrm{AD} = i) - \mathbb{P}(D = 0) \\
&= 1 - \frac{2}{h} \sum_{i=1}^{e-1} \sum_{s=0}^{\frac{h}{2}-i} \frac{\binom{\frac{h}{2}}{s}\binom{\frac{h}{2}}{s+i}}{\binom{h}{2s+i}} - \frac{1}{h} \sum_{s=0}^{\frac{h}{2}} \frac{\binom{\frac{h}{2}}{s}\binom{\frac{h}{2}}{s}}{\binom{h}{2s}}.
\end{aligned}$$

□

**Example.** Table 4.1 shows the probability of imbalance between the two strategies $\mathcal{A}$ and $\mathcal{B}$ for different block lengths. The extent of possible imbalances is limited by the block length, i.e. the maximum imbalance in one center is $h/2$. The assessment whether the possible imbalance $e$ is high depends on the total sample size of patients, e.g. an imbalance of ten patients is high at a sample size of 50 patients but not at a sample size of 5000 patients.

| $h\backslash e$ | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 10 |
|---|---|---|---|---|---|---|---|---|---|
| 2 | 0.500 | 0.500 | - | - | - | - | - | - | - |
| 4 | 0.417 | 0.583 | 0.083 | - | - | - | - | - | - |
| 6 | 0.367 | 0.633 | 0.150 | 0.016 | - | - | - | - | - |
| 8 | 0.332 | 0.668 | 0.204 | 0.039 | 0.004 | - | - | - | - |
| 10 | 0.306 | 0.694 | 0.248 | 0.063 | 0.010 | 0.001 | - | - | - |
| 12 | 0.286 | 0.714 | 0.285 | 0.087 | 0.019 | 0.003 | 0.0002 | - | - |
| 30 | 0.197 | 0.803 | 0.470 | 0.252 | 0.122 | 0.053 | 0.021 | 0.007 | 0.0001 |
| 56 | 0.150 | 0.850 | 0.583 | 0.383 | 0.239 | 0.142 | 0.079 | 0.042 | 0.004 |
| 72 | 0.134 | 0.866 | 0.624 | 0.434 | 0.291 | 0.188 | 0.116 | 0.069 | 0.011 |

Table 4.1: Probabilities for imbalances between strategies in block randomisation greater or equal to $e$ for different block lengths $h$.

### 4.3.2 Stratified randomisation

In contrast to the unstratifeid case, $K$-strata randomisation harbours the risk of up to $K$ unfilled blocks. We will see, that the probability of a strategy imbalance is greater in a clinical trial with stratified blocked randomisation than in a unstratified blocked randomisation. Hallstrom and Davis (1988) describe the probability of total imbalances in a trial using stratified blocked randomisation.

**Lemma 4.3.2.** *Assume $N$ patients should be assigned with equal probability to strategy $\mathcal{A}$ and $\mathcal{B}$, within $K$ strata (centres). Each of the $K$ strata are balanced by using blocks, and the block size in each stratum is $h$. Let $R_i$ be the number of assignments issued in the last block of the $i$th stratum and $r_i$ the realisation of $R_i$, $1 \leq r_i \leq h$. Furthermore, let $S_i$ be the number assigned to strategy $\mathcal{A}$ in that block of the $i$th stratum and $s_i$ the realisation of $S_i$, $1 \leq s_i \leq h/2$. Define*

$$D_i := (R_i - S_i) - S_i = R_i - 2S_i$$

*to be the imbalance in the $i$th stratum. Summing over the independent strata, the total imbalance between the strategies is given by*

$$D = \sum_{i=1}^{K} D_i.$$

*We then have*

$$\mathbb{E}[D_i] = 0, \qquad \mathrm{Var}[D_i] = \frac{h\mathbb{E}[R_i] - \mathbb{E}[R_i^2]}{h-1}$$

*and*

$$\mathbb{E}[D] = 0, \qquad \mathrm{Var}[D] = \sum_{i=1}^{K} \frac{h\mathbb{E}[R_i] - \mathbb{E}[R_i^2]}{h-1}. \tag{4.3}$$

*Proof.* Conditional on $R_i$, $S_i$ obeys, similar to the case with one centre, a hypergeometric

distribution $(S_i \mid R_i = r_i \sim H(h,h/2,r_i))$, with

$$\mathbb{E}[S_i \mid R_i] = \frac{R_i}{2} \qquad \text{and} \qquad \mathrm{Var}[S_i \mid R_i] = \frac{R_i(h-R_i)}{4(h-1)}. \tag{4.4}$$

For the expectations of $D_i \mid R_i$ and $D_i$, we have

$$\mathbb{E}[D_i \mid R_i] = R_i - 2\mathbb{E}[S_i \mid R_i] = 0 \qquad \text{and also} \qquad \mathbb{E}[D_i] = \mathbb{E}[\mathbb{E}[D_i \mid R_i]] = 0.$$

For the variance in the $i$th stratum we obtain

$$\begin{aligned}
\mathrm{Var}[D_i] &= \mathbb{E}\left[\mathrm{Var}[D_i \mid R_i]\right] + \mathrm{Var}\left[\mathbb{E}[D_i \mid R_i]\right] \\
&= \mathbb{E}\left[\mathbb{E}[(R_i - 2S_i)^2 \mid R_i]\right] + 0 \\
&= \mathbb{E}\left[\mathbb{E}[R_i^2 - 4S_iR_i + 4S_i^2 \mid R_i]\right] \\
&= \mathbb{E}\left[R_i^2 - 4R_i\mathbb{E}[S_i \mid R_i] + 4\mathbb{E}[S_i^2 \mid R_i]\right] \\
&= \mathbb{E}\big[-R_i^2 + 4 \underbrace{\mathbb{E}[S_i^2 \mid R_i]}_{=\mathrm{Var}[S_i|R_i]+(\mathbb{E}[S_i|R_i])^2=\mathrm{Var}[S_i|R_i]+R_i^2/4}\big] && \text{with (4.4)} \\
&= \mathbb{E}\left[4\mathrm{Var}[S_i \mid R_i]\right] \\
&= \mathbb{E}\left[\frac{hR_i - R_i^2}{h-1}\right] && \text{with (4.4)} \\
&= \frac{h\mathbb{E}[R_i] - \mathbb{E}[R_i^2]}{h-1}.
\end{aligned}$$

and for the sum of the independent differences in each stratum follows

$$\mathrm{Var}[D] = \mathrm{Var}\left[\sum_{i=1}^{K} D_i\right] = \sum_{i=1}^{K} \mathrm{Var}[D_i] = \sum_{i=1}^{K} \frac{h\mathbb{E}[R_i] - \mathbb{E}[R_i^2]}{h-1}. \qquad \square$$

**Remark.**

- The absolute difference of $\mathrm{AD}_i = |D_i|$ can take values between 0 and $h/2$. The cumulative difference over all strata $\mathrm{AD} = \sum_{i=1}^{K} \mathrm{AD}_i$ lies between 0 and $Kh/2$. Before the probability of the imbalance is calculated, the difference between treated patients in each strategies which is not desired should be determined depending on the sample size, e.g. a difference of 50 patients are a lot in a total of 100 patients but not in 10,000 patients.

- To use the variance formula (4.3) and to determine the probability of imbalances with block size $h$ and number of strata $K$, the first two moments of $R_i$ must be known. Hallstrom and Davis (1988) consider two special cases that simplify these formulas. We present these two different models in the next two lemmas. In the first model, we assume that $R_i$ follows a discrete uniform distribution on the integers 1 to $h$. In the second case, the number of assignments in the last block of the $i$th stratum $R_i$ follows a binomial distribution with parameters $h$ and $p_i$. In general, the block length $h$ is fixed and $hp_i$ is the average number of assignments in the last block.

  Hallstrom and Davis (1988) and Kundt (2002) assume a binomial distribution for the number of assignments in the last block of $i$th stratum $R_i$ with $N$ and $P_i$, the total number of randomised patients and the probability that a patient belongs to

the $i$th stratum. If we assume that no block is filled, this assumption of binomial distribution can be used. Otherwise, this contradicts the definition of $R_i$ as number of assignments issued in the last block of the $i$th stratum, $1 \leq R_i \leq h$.

**Example.** Figure 4.4 shows the observed numbers of assignments in the last blocks $r_i$ and the differences to the mean of all $r_i$ of each centre in the NeSSy study. Based on this database, it is difficult to estimate the first and second moment of $R_i$ for each centre, since we have only one value for one centre. However, if we assume that all $R_i$ are independent and identically distributed, we can estimate the moments with the empirical moment estimators from the 14 centres. We obtain a mean value of 6.36 and a second moment of 77.43 and in total an estimation of $\mathrm{Var}[D]$ with 54.69 ($\sqrt{\mathrm{Var}[D]} = 7.40$). In the same way, we can also estimate $\mathrm{Var}[D_i]$ directly with the imbalances of strategies $d_i$ from all centres ($d_1 = 0$, $d_2 = -1$, $d_3 = -2$, $d_4 = 1$, $d_5 = 2$, $d_6 = 6$, $d_7 = 0$, $d_8 = -1$, $d_9 = 1$, $d_{10} = 1$, $d_{11} = 2$, $d_{12} = 1$, $d_{13} = 1$ and $d_{14} = 0$). We obtain an empirical standard deviation for $D$ of 7.07.

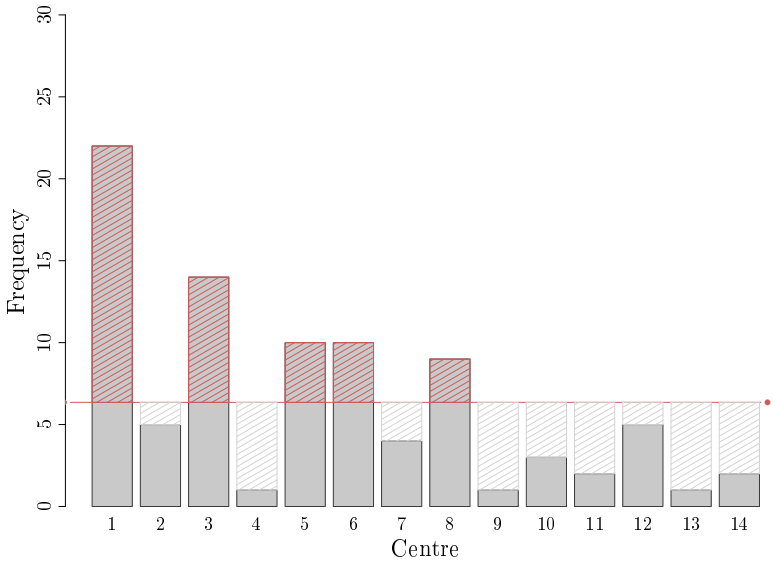



Figure 4.4: Observed numbers of assignments issued in the last block $r_i$ in the NeSSy study, by centre. The striped areas (red and light grey) show the differences to the mean number of patients in each centre.

**Lemma 4.3.3 (First model – uniform distribution).** *Let $R_i$ be uniformly distributed over $\{1, \ldots, h\}$. Then we have*

$$\mathrm{Var}[D] = \frac{K(h+1)}{6}. \tag{4.5}$$

*Proof.* Under the uniform distribution assumption, we have

$$\mathbb{E}[R_i] = \frac{h+1}{2}$$

and

$$\begin{aligned}\mathbb{E}[R_i^2] &= \mathrm{Var}[R_i] + (\mathbb{E}[R_i])^2 \\ &= \frac{h^2-1}{12} + \left(\frac{h+1}{2}\right)^2 \\ &= \frac{h^2-1+3h^2+6h+3}{12} \\ &= \frac{2(2h^2+3h+1)}{12} \\ &= \frac{(h+1)(2h+1)}{6}.\end{aligned}$$

Thus, from Equation (4.3), we get

$$\begin{aligned}\mathrm{Var}[D] &= \frac{1}{h-1}\sum_{i=1}^{K}\left(h\frac{h+1}{2} - \frac{(h+1)(2h+1)}{6}\right) \\ &= \frac{1}{h-1}\sum_{i=1}^{K}\frac{(h-1)(h+1)}{6} \\ &= \frac{K(h+1)}{6}.\end{aligned}$$

□

**Lemma 4.3.4 (Second model – binomial distribution)**. *Let $R_i$ be binomially distributed with parameter $h$ and $p_i$ ($R_i \sim \mathrm{Bin}(h, p_i)$). Then we have*

$$\mathrm{Var}[D] = h\sum_{i=1}^{K} p_i(1-p_i). \tag{4.6}$$

*Proof.* Under the binomial distribution,

$$\mathbb{E}[R_i] = hp_i$$

and

$$\begin{aligned}\mathbb{E}[R_i^2] &= \mathrm{Var}[R_i] + (\mathbb{E}[R_i])^2 \\ &= hp_i(1-p_i) + (hp_i)^2.\end{aligned}$$

From (4.3), we can compute

$$\begin{aligned}\mathrm{Var}[D] &= \sum_{i=1}^{K}\frac{hhp_i - \left(hp_i(1-p_i) + (hp_i)^2\right)}{h-1} \\ &= \sum_{i=1}^{K}\frac{hp_i\left(h - (1-p_i+hp_i)\right)}{h-1} \\ &= h\sum_{i=1}^{K}\frac{p_i(h-1+p_i-hp_i)}{h-1}\end{aligned}$$

$$= h \sum_{i=1}^{K} \frac{p_i(h-1)(-p_i+1)}{h-1}$$
$$= h \sum_{i=1}^{K} p_i(1-p_i). \qquad \square$$

**Remark.** To compute the probability $\mathbb{P}(\text{AD} \geq e)$, for $e \geq 0$, a normal approximation to the distribution of $D$ can be used (Rosenberger and Lachin, 2004, page 57). Assume $D \overset{A}{\sim} \mathcal{N}(0,\text{Var}[D])$, then it follows that $(\text{Var}[D])^{-1/2}D$ is standard normally distributed and

$$\begin{aligned}
\mathbb{P}(\text{AD} \geq e) &= \mathbb{P}(|D| \geq e) \\
&= \mathbb{P}\left(\left|\frac{D}{\sqrt{\text{Var}[D]}}\right| \geq \frac{e}{\sqrt{\text{Var}[D]}}\right) \\
&\simeq \Phi\left(-\frac{e}{\sqrt{\text{Var}[D]}}\right) + 1 - \Phi\left(\frac{e}{\sqrt{\text{Var}[D]}}\right) \\
&= 2\left(1 - \Phi\left(\frac{e}{\sqrt{\text{Var}[D]}}\right)\right).
\end{aligned}$$

The variance $\text{Var}[D]$ as well as this probability depend on the number of strata (centres) $K$ and the block length $h$. In the second model considered above, the probabilities $p_i$ additionally influence $\mathbb{P}(\text{AD} \geq e)$ through $\text{Var}[D]$.

**Example.** In the NeSSy study, there was an imbalance of AD = 11 between the strategies. With the newly derived models, we want to calculate the probability of an imbalance greater than or equal to eleven for the originally planned study sample size and for the actual one. It was planned to recruit 630 patients in $K = 10$ centres at block length $h = 30$, i.e. more than one block was expected to be filled in each stratum. For the uniformly distributed model, we receive the probability $\mathbb{P}(\text{AD} \geq 11) = 0.13$. For the calculation of the probability, we use the normal approximation of the remark above and the Equation (4.5) for the variance of $D$ in the first model. For the second model, we have to make some assumptions on the probabilities $p_i$ of the distribution of each number of assignments issued in the last block of the $i$th stratum $R_i$. For $p_i = 1/2$, we receive $\mathbb{P}(\text{AD} \geq 11) = 0.20$. In the worst case scenario, each block is filled only half and all of the patients of this half block are randomised to one strategy.

In the study performed, 149 patients were recruited in 14 centres, i.e. on average, each centre has recruited 10.64 patients. In this case, we can use the distribution of the observed numbers of assignments in the last block seen in Figure 4.4 for the binomially distributed model. We take in each center the same probability $p_i = \sum_i r_i/(14 \cdot 30) = 0.21$ for $i = 1, \ldots, 14$, the average relative frequency of the number of assignments in the last block, and calculate the variance from Equation (4.6). Thus, we obtain $\mathbb{P}(\text{AD} \geq 11) = 0.19$. With the uniformly distributed model, we receive $\mathbb{P}(\text{AD} \geq 11) = 0.20$. To investigate how well these models describe the reality, we made simulation studies in which the NeSSy study conditions were used with their distribution of patients per center (see Figure 4.5). For the results, 10,000 simulation runs were performed. Figure 4.5 shows the histogram and normal approximation with the mean 74.51 and standard deviation sd = 4.20 of the number of patients in strategy $\mathcal{A}$ from the simulations.

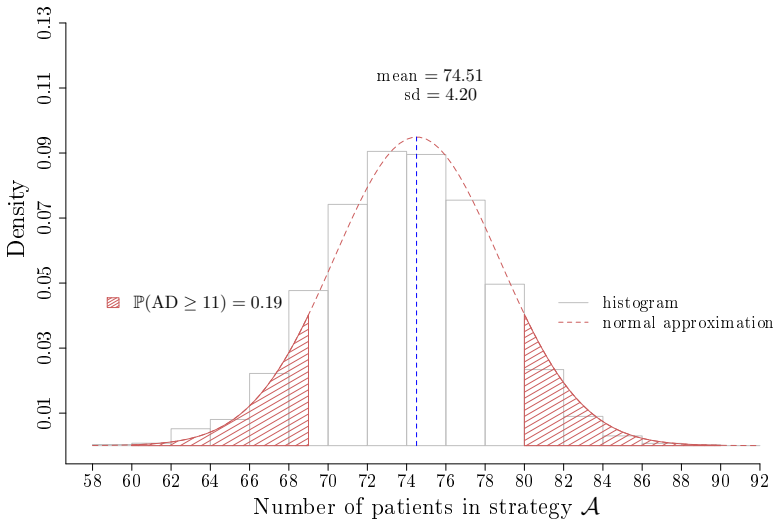



Figure 4.5: Histogram and normal approximation of the distribution of the patients treated with one strategy from a simulation study with NeSSy conditions.

Although AD = 11 is a large difference in a small sample size of 149, the probability to reach this absolute difference is larger than 19%. With the present distribution of patients per centre, a worst case difference of AD = 75 was theoretically possible in the NeSSy study. This number results from the following considerations: We have two full blocks in two centres and these are balanced. Additionally, we have one incomplete block where more than the half of the patients (22 patients) are randomised. Therefore, at least 14 patients are balanced in this block and in total at least 74 patients are balanced in strategies. The remaining patients ($149 - 74 = 75$) may be randomised to only one strategy. In Section 4.5, we discuss modifications of the randomisation list which decrease the probability of strategy imbalances.

If we consider the difference of both strategies, the mean of the difference is equal to zero (see Equation 4.3) and we can concentrate on the standard deviation. Figure 4.6 shows the histogram of difference between both strategies in the simulation studies and the normal approximation with standard deviation from the simulations, the uniform model and the binomial model. The standard deviations from the uniform and binomial model are close to the empirical standard deviations. Hence the theoretical results are consistent with the simulation studies.

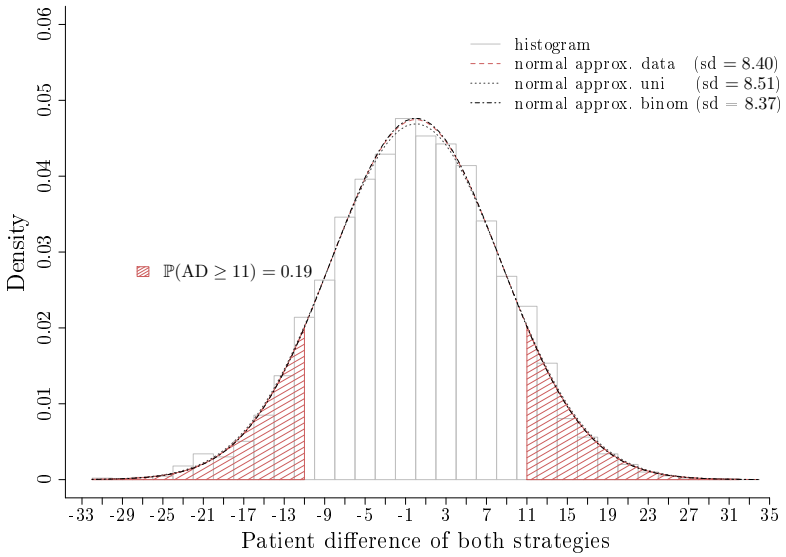



Figure 4.6: Histogram and normal approximation (approx.) of the distribution of differences between both strategies. Normal approximations are calculated with standard deviation from the simulations (data), the uniform model (uni) and the binomial model (binom).

## 4.4 Probability of two-pair combination imbalance

**Example.** To measure the imbalance in the number of appearances of two-pair combinations, we need a parameter which describes the distances of the frequencies of each two-pair combination from the mean value of the frequencies of two-pair combinations.

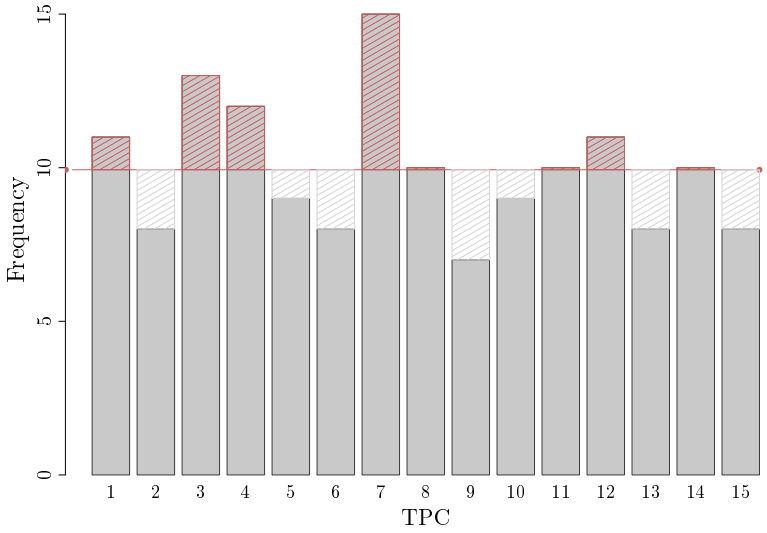



Figure 4.7: Idea for measuring the imbalance in frequencies of two-pair combinations. The striped areas (red and light grey) show the deviations from the mean per two-pair combination.

To introduce such a parameter, we have a look at the NeSSy example with the different frequencies of two-pair combinations (see Figure 4.7). At a number of 149 patients, each of the 15 two-pair combinations should occur $149/15 \approx 9.93$ times. The striped areas in Figure 4.7 show the deviations from the mean. If we average all squared deviations, we obtain a standard deviation of 2.19.

Since we do not have the frequencies of two-pair combinations when planning a study, we will design a model for the expected variance. At first, we have a look at the model for only one centre with one block. Later we will generalize this idea to the case of one center with more blocks and to the stratified blocked randomisation case with $K > 1$ centres.

**Definition 4.4.1 (Variance estimator and average variance estimator).** *Let $X_m$, for $m = 1, \ldots, \tau$, identically and independently distributed random variables with expected value $\mathbb{E}[X_m] < \infty$ and unknown variance $\mathrm{Var}[X_m] < \infty$. $\vec{X} := (X_1, \ldots, X_\tau)$ describes the vector of all $X_m$. Then, we define a variance estimator of $X_m$ as*

$$S^2(\vec{X}) := \frac{1}{\tau} \sum_{m=1}^{\tau} (X_m - \mathbb{E}[X_m])^2$$

*and the average variance estimator of $X_m$ as the expected value of the variance estimator of $X_m$*

$$\mathbb{E}[S^2(\vec{X})] = \frac{1}{\tau} \sum_{m=1}^{\tau} \mathbb{E}\left[(X_m - \mathbb{E}[X_m])^2\right].$$

### 4.4.1 Unstratified randomisation

**Proposition 4.4.2 (Average variance estimator of the two-pair combination frequencies in one block).** *Consider a $\mathrm{POR}_{k,l}$ design with only one block of minimum block length $h := \mathrm{H}_{k,l}^{\mathrm{POR}}$. We denote the number of two-pair combinations in $\mathcal{TPC}_{k,l}$ by $\tau$. Remember that between $h$ and $\tau$, we have the relation $h/2 = \tau$, that means we have two equal two-pair combinations in each block. Let $R$ be the number of assignments issued and $r$ the realisation of $R$, $1 \leq r \leq h$, and let $X_m$, $m = 1, \ldots, \tau$ the number of occurrences of the $m$th two-pair combination. Then, $\vec{X} \mid R = r$ is multivariate hypergeometrically distributed with $H(h,2,\ldots,2,r)$ and the marginal distribution of $X_m \mid R = r$ follows a hypergeometric distribution with $H(h,2,r)$. Furthermore,*

$$\mathbb{E}[S^2(\vec{X})] = \frac{2(h-2)}{h^2(h-1)} \mathbb{E}[R](h - \mathbb{E}[R]) + \frac{2}{h(h-1)} \mathrm{Var}[R]. \tag{4.7}$$

*Proof.* Conditional on $R$, each $X_m$, $m = 1, \ldots, \tau$ describes the draw of $R$ items from a population of size $h$ that has 2 success states in the population. The marginal distribution of $X_m \mid R = r$ follows a hypergeometric distribution with $H(h,2,r)$, which implies

$$\mathbb{E}[X_m \mid R] = \frac{2R}{h} \qquad \text{and} \qquad \mathrm{Var}[X_m \mid R] = \frac{2R(h-2)(h-R)}{h^2(h-1)}. \tag{4.8}$$

For the average variance estimator of $X_m$ we obtain

$$\mathbb{E}[S^2(\vec{X})] = \frac{1}{\tau} \sum_{m=1}^{\tau} \mathbb{E}\left[(X_m - \mathbb{E}[X_m])^2\right]$$

$$= \underbrace{\frac{1}{\tau}\sum_{m=1}^{\tau}}_{=1} \mathrm{Var}[X_m], \quad \text{since} \quad X_m \text{ i.i.d.}$$
$$= \mathrm{Var}[X_m].$$

With the variance decomposition, we compute the variance of $X_m$

$$\begin{aligned}
\mathbb{E}[S^2(\vec{X})] &= \mathbb{E}[\mathrm{Var}[X_m \mid R]] + \mathrm{Var}[\mathbb{E}[X_m \mid R]] \\
&= \mathbb{E}\left[\frac{2R(h-2)(h-R)}{h^2(h-1)}\right] + \mathrm{Var}\left[\frac{2R}{h}\right], \qquad \text{with Equations (4.8)} \\
&= \frac{2(h-2)}{h^2(h-1)}(h\mathbb{E}[R] - \mathbb{E}[R^2]) + \frac{4}{h^2}\mathrm{Var}[R] \\
&= \frac{2(h-2)}{h(h-1)}\mathbb{E}[R] - \frac{2(h-2)}{h^2(h-1)}\mathbb{E}[R^2] + \frac{4}{h^2}\mathrm{Var}[R] \\
&= \frac{2(h-2)}{h(h-1)}\mathbb{E}[R] - \frac{2(h-2)}{h^2(h-1)}\mathrm{Var}[R] - \frac{2(h-2)}{h^2(h-1)}(\mathbb{E}[R])^2 + \frac{4}{h^2}\mathrm{Var}[R] \\
&= \frac{2(h-2)}{h^2(h-1)}\mathbb{E}[R]\,(h - \mathbb{E}[R]) + \frac{2}{h(h-1)}\mathrm{Var}[R]. \qquad \square
\end{aligned}$$

**Conclusion 4.4.3 (First model – uniform distribution).** *If $R$ is uniformly distributed over the integers 1 to $h$, then*

$$\mathbb{E}[S^2(\vec{X})] = \frac{2h^2 - h - 3}{3h^2}.$$

*Proof.* If we assume that $R$ is uniformly distributed, we plug

$$\mathbb{E}[R] = \frac{h+1}{2} \quad \text{and} \quad \mathrm{Var}[R] = \frac{(h+1)(h-1)}{12}$$

into Equation (4.7)

$$\begin{aligned}
\mathbb{E}[S^2(\vec{X})] &= \frac{2(h-2)}{h^2(h-1)}\frac{h+1}{2}\left(h - \frac{h+1}{2}\right) + \frac{2}{h(h-1)}\frac{(h+1)(h-1)}{12} \\
&= \frac{(h-2)(h+1)}{2h^2} + \frac{h+1}{6h} \\
&= \frac{3(h^2 - 2h + h - 2) + h^2 + h}{6h^2} \\
&= \frac{4h^2 - 2h - 6}{6h^2} \\
&= \frac{2h^2 - h - 3}{3h^2}. \qquad (4.9)
\end{aligned}$$

$\square$

**Conclusion 4.4.4 (Second model – binomial distribution).** *Let $R$ be binomially distributed with parameters $h$ and $p$ ($R \sim \mathrm{Bin}\,(h,p)$). Then we have*

$$\mathbb{E}[S^2(\vec{X})] = 2p(1-p). \qquad (4.10)$$

*Proof.* If we assume that $R$ is binomially distributed, we insert

$$\mathbb{E}[R] = hp \quad \text{and} \quad \mathrm{Var}[R] = hp(1-p)$$

into Equation (4.7)

$$\begin{aligned}\mathbb{E}[S^2(\vec{X})] &= \frac{2(h-2)}{h^2(h-1)} hp(h-hp) + \frac{2}{h(h-1)} hp(1-p) \\ &= \frac{2p(1-p)}{h-1}(h-2+1) \\ &= 2p(1-p).\end{aligned}$$

□

**Conclusion 4.4.5.** *Consider a* $\mathrm{POR}_{k,l}$ *design with* $T$ *blocks of length* $h$ *and let* $t \in \{1, \ldots, T-1\}$ *be an arbitrary but fixed number of filled blocks. Then*

1. *the average variance estimator of* $\vec{X}^{t+1} = (X_1^{t+1}, \ldots, X_\tau^{t+1})$*, where* $X_m^{t+1}$ *describes the number of occurrences of* $\mathrm{TPC}_m$ *in the* $(t+1)$*th block, is equal to the average variance estimator in Equation* (4.7)*.*

2. *the average variance estimator of* $\vec{X}^{\mathrm{tot}} = (X_1^{\mathrm{tot}}, \ldots, X_\tau^{\mathrm{tot}})$*, where* $X_m^{\mathrm{tot}}$ *is the number of occurrences of* $\mathrm{TPC}_m$*, is equal to the average variance estimator of* $\vec{X}^{t+1}$*.*

*Proof.*

1. Obviously $\vec{X}^{t+1}$ follows the same distribution as $\vec{X}$ from Proposition 4.4.2. Therefore we have

$$\mathbb{E}[S^2(\vec{X})] = \mathbb{E}[S^2(\vec{X}^{t+1})].$$

2. According to the conditions, the first $t$ blocks are completely filled. Each two-pair combination occurs twice in a filled block. Therefore, we have

$$X_m^{\mathrm{tot}} = X_m^{t+1} + 2t.$$

Consequently, we have

$$\begin{aligned}S^2(\vec{X}^{\mathrm{tot}}) &= \frac{1}{\tau} \sum_{m=1}^{\tau} \left(X_m^{\mathrm{tot}} - \mathbb{E}[X_m^{\mathrm{tot}}]\right)^2 \\ &= \frac{1}{\tau} \sum_{m=1}^{\tau} \left(X_m^{t+1} + 2t - \mathbb{E}[X_m^{t+1}] - 2t\right)^2 \\ &= \frac{1}{\tau} \sum_{m=1}^{\tau} \left(X_m^{t+1} - \mathbb{E}[X_m^{t+1}]\right)^2 \\ &= S^2(\vec{X}^{t+1}).\end{aligned}$$

Thus, for the average variance estimators, we obtain the required equality

$$\mathbb{E}[S^2(\vec{X}^{\mathrm{tot}})] = \mathbb{E}[S^2(\vec{X}^{t+1})].$$

□

### 4.4.2 Stratified randomisation

In this section, we consider the average variance estimator of two-pair combination frequencies if we have $K > 1$ centres (strata). For this purpose, we have to extent the previous considerations from one stratum of $K$ strata.

**Conclusion 4.4.6.** *Assume $N$ patients should be assigned with equal probability to each two-pair combination, within each of the $K$ strata (centres). The two-pair combinations are balanced in each stratum, and the block size in each stratum is $h := \mathrm{H}_{k,l}^{\mathrm{POR}}$. Let $R_i$ be the number of assignments issued in the last block of the $i$th stratum, and let $r_i$ be the realisation of $R_i$, $1 \leq r_i \leq h$. Furthermore, let $X_{mi}$ be the number of assignments to the $m$th two-pair combination in the last block of the $i$th stratum and $x_{mi}$ the realisation of $X_{mi}$, $0 \leq x_{mi} \leq 2$. Furthermore, let $\vec{X}_m = (X_{m1}, \ldots, X_{mK})$ be the vector of random variables describing the number of assignments to the mthe two-pair combinations in all strata. Then we have for the average variance estimator of $\vec{X}_1, \ldots, \vec{X}_K$*

$$S^2(\vec{X}_1, \ldots, \vec{X}_K) := \frac{1}{\tau} \sum_{m=1}^{\tau} \sum_{i=1}^{K} (X_{mi} - \mathbb{E}[X_{mi}])^2$$

*of the two-pair combinations*

$$\mathbb{E}[S^2(\vec{X}_1, \ldots, \vec{X}_K)] = \sum_{i=1}^{K} \left( \frac{2(h-2)}{h^2(h-1)} \mathbb{E}[R_i](h - \mathbb{E}[R_i]) + \frac{2}{h(h-1)} \mathrm{Var}[R_i] \right). \tag{4.11}$$

*Proof.* In the same manner as before, we obtain with $X_{mi} \mid R_i = r_i \sim H(h, 2, r_i)$

$$\begin{aligned}
\mathbb{E}[S^2(\vec{X}_1, \ldots, \vec{X}_K)] &= \underbrace{\frac{1}{\tau} \sum_{m=1}^{\tau}}_{=1} \sum_{i=1}^{K} \mathbb{E}\left[ (X_{mi} - \mathbb{E}[X_{mi}])^2 \right] \\
&= \sum_{i=1}^{K} \mathbb{E}\left[ (X_{1i} - \mathbb{E}[X_{1i}])^2 \right] \\
&= \sum_{i=1}^{K} \left( \frac{2(h-2)}{h^2(h-1)} \mathbb{E}[R_i](h - \mathbb{E}[R_i]) + \frac{2}{h(h-1)} \mathrm{Var}[R_i] \right).
\end{aligned}$$

□

**Conclusion 4.4.7 (First model – uniform distribution).** *Let $R_i$ be uniformly distributed over $\{1, \ldots, h\}$. Then we have*

$$\mathbb{E}[S^2(\vec{X}_1, \ldots, \vec{X}_K)] = \frac{K(2h^2 - h - 3)}{3h^2}. \tag{4.12}$$

*Proof.* Under the uniform distribution assumption, we have

$$\mathbb{E}[R_i] = \frac{h+1}{2} \quad \text{and} \quad \mathrm{Var}[R_i] = \frac{(h+1)(h-1)}{12}.$$

Therefore, from Equations (4.11) and (4.9) follows that

$$\mathbb{E}[S^2(\vec{X}_1, \ldots, \vec{X}_K)] = \frac{K(2h^2 - h - 3)}{3h^2}.$$

□

**Conclusion 4.4.8 (Second model – binomial distribution).** *Let $R_i$ be binomially distributed with parameters $h$ and $p_i$ ($R_i \sim \text{Bin}\,(h, p_i)$). Then we have*

$$\mathbb{E}[S^2(\vec{X}_1, \ldots, \vec{X}_K)] = 2\sum_{i=1}^{K} p_i(1-p_i). \tag{4.13}$$

*Proof.* Under the binomial distribution, we have

$$\mathbb{E}[R_i] = hp_i \quad \text{and} \quad \text{Var}[R_i] = hp_i(1-p_i).$$

From (4.11), we can compute $\mathbb{E}[S^2(\vec{X}_1, \ldots, \vec{X}_K)]$

$$\begin{aligned}
\mathbb{E}[S^2(\vec{X}_1, \ldots, \vec{X}_K)] &= \sum_{i=1}^{K} \left( \frac{2(h-2)}{h^2(h-1)} hp_i(h-hp_i) + \frac{2}{h(h-1)} hp_i(1-p_i) \right) \\
&= \sum_{i=1}^{K} \frac{2p_i(1-p_i)}{h-1}(h-2+1) \\
&= 2\sum_{i=1}^{K} p_i(1-p_i). \qquad \square
\end{aligned}$$

**Remark.** To compute the probability $\mathbb{P}(|X_m - \mathbb{E}[X_m]| \geq e_2)$, for $e_2 \geq 0$, the normal approximation can be used (Rosenberger and Lachin, 2004, page 57). Assume $X_m - \mathbb{E}[X_m] \overset{A}{\sim} \mathcal{N}(0,\sigma^2)$, in which $\sigma^2$ is estimated by the average variance of the two-pair combination frequencies. Then $(\mathbb{E}[S^2(\vec{X}_1, \ldots, \vec{X}_K)])^{-1/2}(X_m - \mathbb{E}[X_m])$ follows a standard normal distribution and

$$\begin{aligned}
\mathbb{P}(|X_m - \mathbb{E}[X_m]| \geq e_2) &= \mathbb{P}\left( \left| \frac{X_m - \mathbb{E}[X_m]}{\sqrt{\mathbb{E}[S^2(\vec{X}_1, \ldots, \vec{X}_K)}} \right| \geq \frac{e_2}{\sqrt{\mathbb{E}[S^2(\vec{X}_1, \ldots, \vec{X}_K)}} \right) \\
&\simeq \Phi\left( -\frac{e_2}{\sqrt{\mathbb{E}[S^2(\vec{X}_1, \ldots, \vec{X}_K)}} \right) + 1 - \Phi\left( \frac{e_2}{\sqrt{\mathbb{E}[S^2(\vec{X}_1, \ldots, \vec{X}_K)}} \right) \\
&= 2\left( 1 - \Phi\left( \frac{e_2}{\sqrt{\mathbb{E}[S^2(\vec{X}_1, \ldots, \vec{X}_K)}}) \right) \right).
\end{aligned}$$

The probability respectively the variance depend on the number of strata (centres) $K$ and the block length $h$. In the second model the probabilities $p_i$ additionally influence $\mathbb{P}(|X_m - \mathbb{E}[X_m]| \geq e_2)$.

**Example.** In order to compare the different models for the imbalances between two-pair combination frequencies, we come back to our simulation studies in which we used the NeSSy study conditions including the same distribution of patients per center (see Figure 4.5). The simulation was run 10,000 times and yielded a mean of 9.93 and a standard deviation 2.13 for the frequencies of two-pair combinations. Figure 4.8 shows the histogram and the normal approximations of the frequencies of occurrence of the two-pair combinations from the simulation study, the uniform model and the binomial model. The standard deviation of the uniformly distributed model is approximately 3.03. For the

second model, we take the same probability $p_i = \sum_i r_i/(14 \cdot 30) = 0.21$ for $i = 1, \ldots, 14$ in each center, the average relative frequency of the number of assignments in the last block. Hence we receive a standard deviation of the binomially distributed model of 2.16 which is close to the empirical standard deviation.

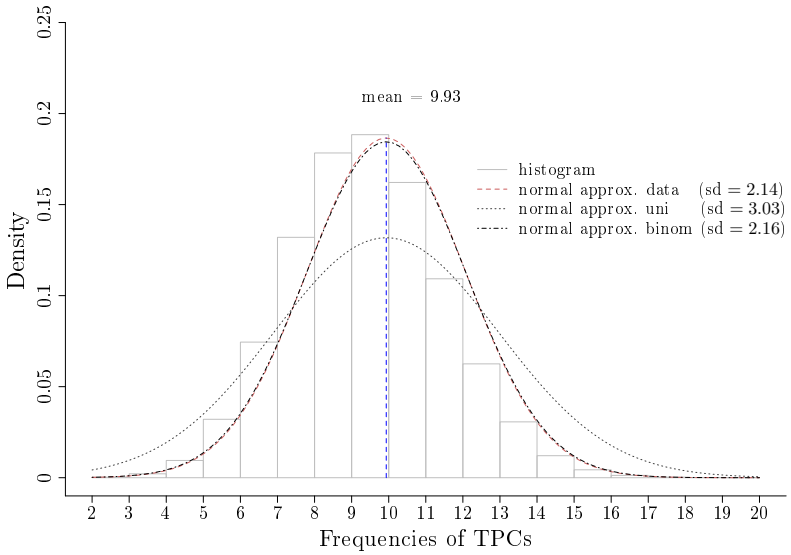



Figure 4.8: Histogram of the two-pair combination frequencies and the normal approximation with standard deviation from a simulation study with NeSSy conditions, uniform model (uni) and binomial model (binom).

**Remark.** The concept of two-pair combination imbalance outlined above can not only be considered in this context. Rather, it is the generalisation of imbalance between two treatments to $\tau$ treatments. The only adjustment which has to be made is the number of treatments in one block (here it is two).

## 4.5 Possible modifications of randomisation lists

### 4.5.1 Modification I

As Pocock (1982) described, 'to achieve successful balances [in the standard method of stratification, the block randomisation within strata] the block size should not to be too large, say blocks of 4 or 6 with 2 treatments, and the number of strata should not to be too great'. Usually, we do not have any influence on the number of centres since in practice, a certain number of centres is needed to achieve the preplanned sample size. Nevertheless, attempts should be made to keep this number as low as possible. Likewise, we do not have the possibility to change the minimum block length $\mathrm{H}_{k,l}^{\mathrm{POR}}$, because it is determined by the number of two-pair combinations. Our main aim is to avoid imbalances between strategies because this may affect the power of a statistical test. For example, the power of the $t$-test for the difference in means of two groups is maximised with equal sample sizes (see Lachin (1988) and Appendix of White and Freedman (1978)). We can reach this aim with one modification to the randomisation list. For this we consider the $\mathrm{POR}_{2,2}$ design as an example.

**Example.** The $\mathrm{POR}_{2,2}$ design has a minimum block length of $\mathrm{H}_{2,2}^{\mathrm{POR}} = 12$. Each block in the random list consists of six tuples with strategy $\mathcal{A}$ and six tuples with strategy $\mathcal{B}$. If the entire block is used, both strategies are balanced. But we could even design a randomisation list in which both strategies are balanced after each 6, 4 and 2 two-pair combinations. To this end, we define the sub block length $h_j$ with $\mathrm{H}_{2,2}^{\mathrm{POR}} = \sum_{j=1}^{J} h_j$, $j = 1, \ldots, J$, where $J$ is the quotient of minimum block length $\mathrm{H}_{2,2}^{\mathrm{POR}}$ and sub block length $h_j$. We assume that $h_j = h_{j'}$ for $j \neq j'$. Table 4.2 shows the possibilities of sub blocks in the $\mathrm{POR}_{2,2}$ design.

| Possibility | Number of sub blocks | Sub blocks length |
|---|---|---|
| 1 | 1 | $h_1 = 12$ |
| 2 | 2 | $h_1 = 6$, $h_2 = 6$ |
| 3 | 3 | $h_1 = 4$, $h_2 = 4$, $h_3 = 4$ |
| 4 | 6 | $h_1 = 2$, $h_2 = 2$, $h_3 = 2$, $h_4 = 2$, $h_5 = 2$, $h_6 = 2$ |

Table 4.2: Possibilities of sub blocks in the $\mathrm{POR}_{2,2}$ design.

As may be seen in Table 4.1 for one centre $\mathbb{P}(\mathrm{AD} \geq e)$, $e \geq 1$, is largest for $h_j = 12$ and becomes smaller with decreasing block length.

With this approach, the minimum block length is maintained. We carry an additional restriction for the randomisation list, that we have a good balance between the strategies in unfilled blocks.

**Definition 4.5.1 (Sub block length).** *Consider a* $\mathrm{POR}_{k,l}$ *design. Then a sub block length* $h_j$ *of* $\mathrm{H}_{k,l}^{\mathrm{POR}}$ *is every even number in the set of divisors of the minimum block length* $\mathrm{H}_{k,l}^{\mathrm{POR}}$. *We have*

$$\mathrm{H}_{k,l}^{\mathrm{POR}} = \sum_{j=1}^{J} h_j = J \cdot \ h_j,$$

*where* $J$ *is the quotient of minimum block length* $\mathrm{H}_{k,l}^{\mathrm{POR}}$ *and sub block length* $h_j$.

**Remark.** For the distribution of the imbalance between the strategies, we use the theory from Section 4.3 and use instead of the minimum block length, the sub block length. The suitability for the corresponding sub block length should therefore be considered in advance. It should be taken into account that a small sub block length has the disadvantage that the physician can predict at the end of each block what the next strategy will be if he knows that there are balanced sub blocks. Although the risk of this is very low in double-blind studies, one should avoid small block sizes such as two. Two standard procedures will also be used in order to reduce the predictability: firstly, the sub block length can be changed at random from one minimum block to the next and secondly, the physician should preferably not be informed that a sub blocking is being used in particular they should not know the sub block size (Pocock, 1979).

**Example.** Theoretically, the standard deviation of the difference $D$ between the two strategies becomes smaller with smaller block length. We performed different simulation studies under the NeSSy conditions with different sub block lengths. The results are shown in Figure 4.9. We can conclude that by using a sub block length smaller than the minimum block length, already a great improvement in the probability of strategy differences

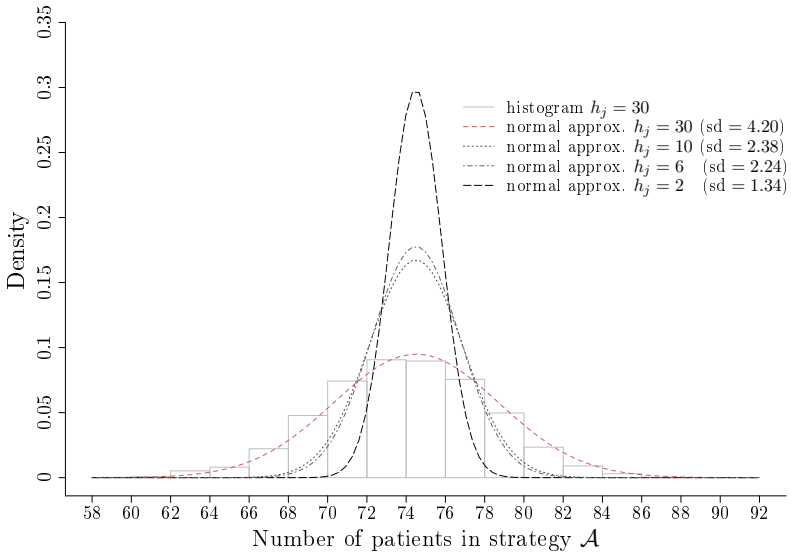



Figure 4.9: Histogram of frequencies of patients treated with strategy $\mathcal{A}$ and normal approximation (approx.) with standard deviations of strategy differences from simulation studies with different sub block lengths $h_j = 30$, $h_j = 10$, $h_j = 6$ and $h_j = 2$ used in the randomisation list.

is conceded. However, the difference between the sub block lengths $h_j = 10$ and $h_j = 6$ is not large. In order to prevent the predictability, we advocate for the sub block length $h_j = 10$, in the $\text{POR}_{2,3}$ design used here.

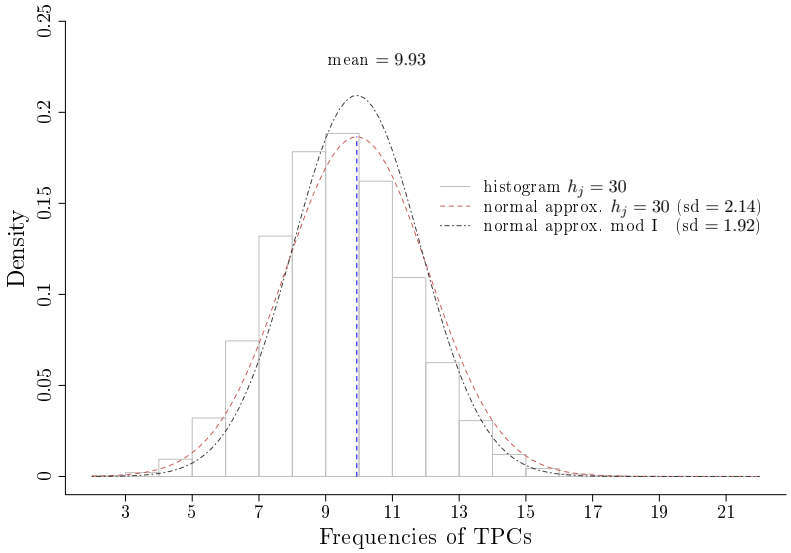



Figure 4.10: Histogram of the two-pair combination frequencies and normal approximation (approx.) of the two-pair combination frequencies with standard deviation from simulation studies with previous randomisation list and with randomisation lists with modification I.

Figure 4.10 shows the results of the simulations described above for the frequencies of two-pair combinations. As we can see, also an improvement in the standard deviation of the frequencies of occurrence of the two-pair combinations was conceded by introducing sub blocks in the randomisation. The improvement is the same for different sub block length $h_j$.

### 4.5.2 Modification II

Our second aim is avoiding imbalances between the frequencies of two-pair combinations. Achieving this goal is much more difficult than balancing between strategies because the number of the different two-pair combinations is larger compared to the number of strategies. This problem is not serious if we have one centre and execute the minimum block length in succession. If the complete block is not used, the maximum differences between the frequencies of two-pair combinations can at most be two, e.g. if one two-pair combination was assigned twice, once for strategy $\mathcal{A}$ and once for strategy $\mathcal{B}$ and the other two-pair combinations was not assigned. In the stratified case, each stratum can achieve a difference of two between the two-pair combination frequencies. In the worst case scenario, the same two-pair combinations are assigned, respectively unassigned, in each of the $K$ strata. This results in the maximum imbalance possible between the frequencies of two-pair combinations of $2K$. To reduce the probability of great imbalances between the frequencies of two-pair combinations, we perform a further modification in the preparation of the randomisation list that after a certain number of randomised patients, the frequencies of two-pair combinations of all strata are balanced as in a Latin square. To make the idea clear, we consider the $\mathrm{POR}_{2,2}$ design as an example.

**Example.** We construct a random list H with minimum block length $\mathrm{H}_{2,2}^{\mathrm{POR}} = 12$ for one centre such that H is divided into three sub blocks $h_1$, $h_2$ and $h_3$ each of block length four with the restriction that both strategies occur equally often in each sub block. We assume for the sake of simplicity that we have a number of three centres indicated by $C_1$, $C_2$ and $C_3$. Now we create for each of the three centres one random list with minimum block length $\mathrm{H}_{2,2}^{\mathrm{POR}}$ and rearrange the three sub blocks $h_1$, $h_2$ and $h_3$ in such a way that all sub blocks of the three overall blocks result in a Latin square (see Table 4.3).

| Centres | $C_1$ | $C_2$ | $C_3$ |
|---|---|---|---|
| | $h_1$ | $h_2$ | $h_3$ |
| H | $h_3$ | $h_1$ | $h_2$ |
| | $h_2$ | $h_3$ | $h_1$ |

Table 4.3: Modification II: Latin square with sub blocks.

However, the two-pair combinations in each sub block are also randomised and for this reason, we have a different ordering in each overall block. The assignment of the overall blocks H to the three centres may be random. By the arrangement of the sub blocks in a Latin square, one overall block is still filled although maybe only four patients are randomised in each centre.

**Example.** In the NeSSy simulation studies, we also used the modification outlined here with a sub block length $h_j = 10$ for one random list. Figure 4.11 shows the results of the simulations studies with NeSSy conditions. The simulation studies with the original randomisation list has the largest standard deviation. Introducing sub blocks (as was done

in the previous section, modification I) leads to a smaller standard deviation than the original randomisation list. The maximum reduction of standard deviation is realised with modification II outlined here.

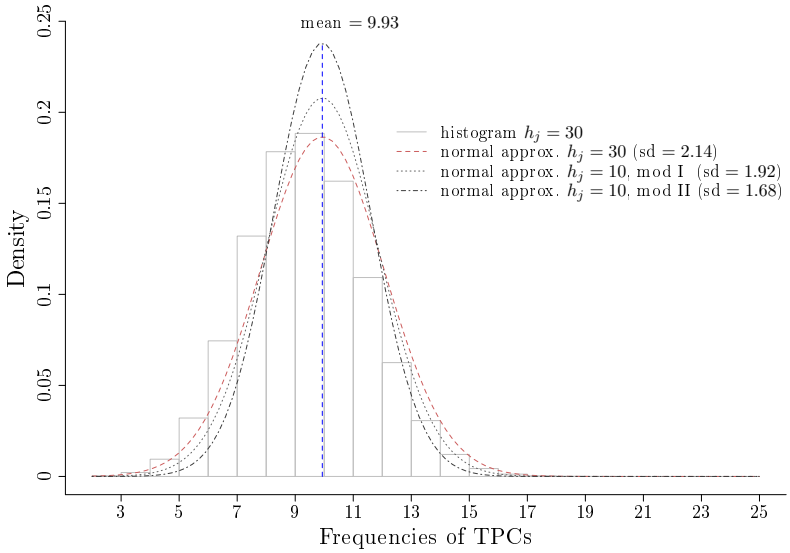



Figure 4.11: Histogram of the two-pair combination frequencies and normal approximation (approx.) of the two-pair combinations frequencies with standard deviation from NeSSy simulation studies with previous randomisation list and with randomisation lists with modification I and II ($h_j = 10$).

**Remark.**

- In order to prevent the predictability, the use of a Latin square should not be known to the physicians.
- The balance behaviour between the strategies is not improved merely by the step from introducing sub blocks (modification I) to arranging these in a Latin square (modification II).

### 4.5.3 Summary modification

The results of this section should be kept in mind when planning a new trial. The probability of imbalances should be checked under the given conditions (sample size, number of treatments and centres, block size) during the planning phase. If these theoretical considerations raise no concerns for large imbalances, there is no need for the use of one of the two presented modifications. The assignments of treatments in both modifications of the random list are fully random and the benefits of randomisation (cf. Schulz and Grimes (2002)) still exist. However, both modifications restrict the randomisation list more than the original one.

If the theoretical considerations demonstrate concerns for large imbalances as well as influence on the results of the statistical analysis, one of the modification methods should be used. Both restricted randomisation modifications control the probability of obtaining

an allocation sequence with an undesirable sample size imbalance. Modification I reduces the imbalance in the strategy groups as well as in the frequencies of two-pair combinations. Moving from modification I to modification II only leads to the improvement of the imbalance in the two-pair combination frequencies. Because of the main focus in this patient-oriented randomisation design is strategy comparison, modification I is definitely an option worth considering in the planning of a trial. To generate an unpredictable randomised allocation sequence, the sub block length should be selected not too small—as mentioned before. To evaluate the different sub block lengths the presented considerations could be taken into account.

CHAPTER 5

# STATISTICAL ANALYSIS

## 5.1 Introduction

The main goal of the $\text{POR}_{k,l}$ design is to compare the strategies, but the design also allows us to test the differences in treatment means of the outcome between the patients who received the treatment solely due to randomisation (randomised choice treated patients) and those where the treatment choice was patient-oriented (patient-oriented treated patients). This test can be performed in each treatment, each strategy, or overall as well. Furthermore, the differences between strategies can be analysed for subgroups consisting of only randomised choice treated patients or only patient-oriented choice treated patients. In this case, we can test our assumptions about the efficacy of strategies, taking heterogeneity of patient-drug-interaction by physician's decision into account.

In order to be able to formulate the according hypotheses and tests, we first introduce a suitable statistical model (one-way classification) as well as the concept of contrast testing. Both are well known, but are briefly reviewed here, to specify the notation used in our considerations for the $\text{POR}_{k,l}$ design. The content of this part is based on Kirk (1995) and Winer et al. (1991). After the basic concepts and notation have been introduced we will discuss which contrasts are of particular interest in the $\text{POR}_{k,l}$ design. Primarily, we are interested in a contrast comparing two different strategies. Beside the main contrast we are also interested in contrasts comparing the treatment effects of only randomised choice treated patients and patient-oriented choice treated patients. Afterwards, we consider the sample size calculation and how the sample size changes if the treatments' sample sizes differ. In the last section, we will examine the influence of the physicians' patient-oriented decision and of the heterogeneous populations on this main contrast for the three different study approaches (POR, Block and CUtLASS design) taking the case of two strategies and two treatments in each strategy as example.

## 5.2 Model

In a clinical trial, we often have a response $Y$ depending on different factors like the effectiveness of treatments or sex. A factor is a categorical variable which can realise in several categories (called 'levels' in the sequel). The goal is to analyse the effects of levels of factors on the mean of $Y$. In this thesis, we assume that the response $Y$ is normally distributed. The case of a discrete response is not considered here.

In our specific case, the clinical trial focuses on a strategy comparison $\mathcal{A}$ vs. $\mathcal{B}$ with

different treatments $A_1, \ldots, A_k$ respectively $B_1, \ldots, B_l$ where the sample size per treatment differs in the most cases. In our case 'treatment' is the factor of interest. Because of the unequal numbers of patients per treatment we consider a model which accounts for this unbalanced design. In order to focus on the main aspects, we assume in this thesis that treatment is the only influencing factor. The model presented below can be extended to multiple factors and multiple covariates as shown by Kirk (1995) and Winer et al. (1991).

To model the influence of strategy as well as treatments on $Y$ (e.g. a score measuring quality of life) use an unbalanced one-way classification or a so-called one-way analysis of variance with fixed-effects. For the purpose of strategy comparison an alternative factor to use in our model would be 'strategy' (with levels $\mathcal{A}$ and $\mathcal{B}$). However, we are also interested in comparing the patient-oriented and not patient-oriented decisions within treatments. This can not be investigated by using the factor strategy. Additionally, it is sensible to assume that different treatments within one strategy have a different influence on $Y$. Therefore, we prefer to use the factor treatment (with levels $A_1, \ldots, A_k, B_1, \ldots, B_l$). This allows us to investigate differences between strategies as well as treatments by using appropriate contrasts (see Section 5.3).

**Definition 5.2.1 (Unbalanced one-way classification with fixed-effects for a $\mathbf{POR_{k,l}}$ design).** *The model equation for an unbalanced one-way classification with fixed-effects for the* $\mathrm{POR}_{k,l}$ *design is*

$$Y_{ji} = \mu_j + \varepsilon_{ji} \qquad \textit{for} \quad i = 1, \ldots, n_j; \quad j \in \mathcal{A} \cup \mathcal{B} \tag{5.1}$$

*where*

- $Y_{ji}$ *is the response for subject* $i$ *in treatment level* $j$ *(random variable with* $\mathbb{E}[Y_{ji}] = \mu_j$*).*
- $\mu_j$ *is the treatment group mean of treatment* $j$ *(parameter in* $\mathbb{R}$*).*
- $\varepsilon_{ji}$ *is the error associated with* $Y_{ji}$ *(random variable).*
- $n_j$ *is the number of patients treated with treatment* $j$*.*

*For the fixed-effects model assumption, the model Equation* (5.1) *contains all the sources of variation that affect* $Y_{ji}$*. The treatment means* $\mu_j$ *for* $j \in \mathcal{A} \cup \mathcal{B}$ *are constant. The only source of variation is the error* $\varepsilon_{ji}$*. We assume that the* $\varepsilon_{ji}$ *are normally and independently distributed with mean equal to zero and variance equal to* $\sigma_\varepsilon^2$*, i.e.* $\varepsilon_{ji} \overset{i.i.d.}{\sim} \mathcal{N}(0, \sigma_\varepsilon^2)$ *,* $i = 1, \ldots, n_j$ *and* $j \in \mathcal{A} \cup \mathcal{B}$*, and* $\sigma_\varepsilon^2$ *is referred to as error variance.*

To express the effect of each level we decompose the expected value $\mathbb{E}[Y_{ji}] = \mu_j$ into

$$\mu_j = \mu + \tau_j,$$

where

- $\mu$ is the expected value of the overall population.
- $\tau_j$ is the treatment effect of $j$th treatment.

Additionally, for the uniqueness of the decomposition, $\sum_{j \in \mathcal{A} \cup \mathcal{B}} \tau_j = 0$ has to be fulfilled. In this way, we have the following model

$$Y_{ji} = \mu + \tau_j + \varepsilon_{ji} \qquad \text{for} \quad i = 1, \ldots, n_j; \; j \in \mathcal{A} \cup \mathcal{B}.$$

According to this equation the realisations $y_{ji}$ of the random variable $Y_{ji}$ can be decomposed

$$\begin{array}{ccccccc} y_{ji} & = & \underbrace{\bar{y}_{..}} & + & \underbrace{(\bar{y}_{j.} - \bar{y}_{..})} & + & \underbrace{(y_{ji} - \bar{y}_{j.})} \\ y_{ji} & = & \hat{\mu} & + & \hat{\mu}_j - \hat{\mu} & + & e_{ji} \\ \text{Score} & & \text{Grand mean} & & \text{Treatment effect} & & \text{Residual effect} \end{array} \tag{5.2}$$

where

$$\bar{y}_{j.} := \frac{1}{n_j} \sum_{i=1}^{n_j} y_{ji} \quad \text{is the mean in treatment level } j$$

$$\bar{y}_{..} := \frac{1}{N} \sum_{j \in \mathcal{A} \cup \mathcal{B}} \sum_{i=1}^{n_j} y_{ji} \quad \text{is the grand mean}$$

with $N = n_{A_1} + \cdots + n_{A_k} + n_{B_1} + \cdots + n_{B_l}$ the total number of observations. Hence, we obtain $\bar{y}_{j.} - \bar{y}_{..}$ for the estimation of $\tau_j$ and $\bar{y}_{..}$ as estimate for the expected value of the overall population $\mu$. The decomposition of the realisations provide a decomposition of the total sum of squares

$$\mathrm{SS}_{\mathrm{TOT}} := \sum_{j \in \mathcal{A} \cup \mathcal{B}} \sum_{i=1}^{n_j} (y_{ji} - \bar{y}_{..})^2$$

into the sum of squares between groups

$$\mathrm{SS}_{\mathrm{BG}} := \sum_{j \in \mathcal{A} \cup \mathcal{B}} n_j \, (\bar{y}_{j.} - \bar{y}_{..})^2$$

and the sum of squares within groups

$$\mathrm{SS}_{\mathrm{RES}} := \sum_{j \in \mathcal{A} \cup \mathcal{B}} \sum_{i=1}^{n_j} (y_{ji} - \bar{y}_{j.})^2.$$

The desired partition of the total sum of squares

$$\begin{array}{ccccc} \mathrm{SS}_{\mathrm{TOT}} & = & \mathrm{SS}_{\mathrm{BG}} & + & \mathrm{SS}_{\mathrm{RES}} \\ \displaystyle\sum_{j \in \mathcal{A} \cup \mathcal{B}} \sum_{i=1}^{n_j} (y_{ji} - \bar{y}_{..})^2 & = & \displaystyle\sum_{j \in \mathcal{A} \cup \mathcal{B}} n_j \, (\bar{y}_{j.} - \bar{y}_{..})^2 & + & \displaystyle\sum_{j \in \mathcal{A} \cup \mathcal{B}} \sum_{i=1}^{n_j} (y_{ji} - \bar{y}_{j.})^2 \end{array} \tag{5.3}$$

is obtained by rearranging the terms in Equation (5.2). A proof can be seen for example in Kirk (1995, pp. 80–83). The partition of the total sum of squares in Equation (5.3) provides an intuitive understanding of the sources of variation. The sum of squares between groups shows the variation between patients treated with different treatments. Nevertheless, the responses of patients in the same treatment level can vary due to the individual differences of the patients. The sum of squares within groups shows the variation due to differences among patients who receive the same treatment. If the sum of squares within groups is small in comparison to the sum of squares between groups, the total variation of the responses of patients can be explained through the variation between groups treated with different treatments rather than through the variation within groups due to the individual

patients. If we assume that the treatment means within the strategies differ, then using the factor 'strategy' instead of 'treatment', the variation between treatments would be at least partially ascribed to the variation within the strategies. This shows another advantage of using treatments as factor in presence of heterogeneous treatment means within strategies.

The degrees of freedom df associated with $SS_{TOT}$, $SS_{BG}$ and $SS_{RES}$ refer to the number of observations whose values are free to vary in this sum of squares. They are only mentioned here, but not determined. The degrees of freedom associated with $SS_{TOT}$ are $df_{TOT} = N - 1$, $df_{BG} = k + l - 1$ are associated with $SS_{BG}$ and with $SS_{RES}$ $df_{RES} = N - (k + l)$ are associated. Corresponding to the partition of the total sum of squares in Equation (5.3), the degrees of freedom of $SS_{BG}$ and $SS_{RES}$ sum up to the degrees of freedom of $SS_{TOT}$, i.e.

$$df_{TOT} = df_{BG} + df_{RES}.$$

Dividing a sum of squares by its degrees of freedom gives mean squares ($MS_{TOT}$, $MS_{BG}$ and $MS_{RES}$).

For the next considerations, we define the parameter

$$\sigma_\mu^2 = \frac{\sum_{j \in \mathcal{A} \cup \mathcal{B}} (\mu_j - \mu)^2}{k + l - 1}$$

which indicates the extent to which the treatment effect differs between the groups. We obtain for the expected value of the mean squares within groups

$$\mathbb{E}[MS_{RES}] = \sigma_\varepsilon^2. \tag{5.4}$$

For the expected value of the mean squares between groups, it can be shown that

$$\mathbb{E}[MS_{BG}] = \sigma_\varepsilon^2 + \frac{N^2 - \sum_{j \in \mathcal{A} \cup \mathcal{B}} n_j^2}{N(k + l - 1)} \sigma_\mu^2 \tag{5.5}$$

(Graybill, 1961, pp. 353–354). The expected value of the total mean square can be obtained by the partition of the total sum of squares and Equations (5.4) and (5.5),

$$\mathbb{E}[MS_{TOT}] = \sigma_\varepsilon^2 + \frac{N^2 - \sum_{j \in \mathcal{A} \cup \mathcal{B}} n_j^2}{N(N - 1)} \sigma_\mu^2.$$

Hence, for the case of equal sample sizes, i.e. $n_j = n$ for all $j \in \mathcal{A} \cup \mathcal{B}$, $N = (k + l)n$ and $\sum_{j \in \mathcal{A} \cup \mathcal{B}} n_j^2 = (k + l)n^2$ we obtain for the expected value of the mean squares

$$\begin{aligned} \mathbb{E}[MS_{BG}] &= \sigma_\varepsilon^2 + n\sigma_\mu^2, \\ \mathbb{E}[MS_{RES}] &= \sigma_\varepsilon^2 \end{aligned}$$

and

$$\mathbb{E}[MS_{TOT}] = \sigma_\varepsilon^2 + \frac{n(k + l - 1)}{n(k + l) - 1} \sigma_\mu^2.$$

The question that immediately arises is whether the differences in treatment effects are due to the (randomly) selected sample or due to the differences in treatments. The null and the two-sided alternative hypotheses can be stated in terms of the population treatment

group means as follows

$$H: \quad \mu_{A_1} = \mu_{A_2} = \cdots = \mu_{B_l} = 0 \quad \text{vs.} \quad K: \quad \mu_j \neq \mu_{j'} \quad \text{for some } j \text{ and } j'.$$

This null hypothesis is also called omnibus hypothesis. Based on the null hypothesis, $\sigma_\mu^2$ will be zero in Equation (5.5). If a treatment effect exists, then the expected value of the mean square between groups estimates the population error variance $\sigma_\varepsilon^2$ plus a function of squared treatment effects. We can asses the magnitude of the treatment effect by setting the treatment effect in relation to the population error variance. Therefore, the statistic

$$F = \frac{\mathrm{MS_{BG}}}{\mathrm{MS_{RES}}}$$

may be used to test the null hypothesis that the treatment effects are equal. If the null hypothesis is true and if the assumption for the fixed-effect model from Definition 5.2.1 are tenable, the statistic $F$ is centrally $F$-distributed with $\mathrm{df_{BG}}$ and $\mathrm{df_{RES}}$ degrees of freedom. The decision rule is as follow: We reject $H$ if the value of the $F$-statistic is larger than the $(1-\alpha)$-quantile of the $F$-distribution with $\mathrm{df_{BG}} = k+l-1$ and $\mathrm{df_{RES}} = N-(k+l)$ degrees of freedom $F_{1-\alpha}(\mathrm{df_{BG}}, \mathrm{df_{RES}})$, otherwise we do not reject $H$. If the null hypothesis of equality of treatment effects is rejected, we are usually interested in the problem of deciding which of the treatment effects are not equal respectively not equal to zero. For this analysis, the concept of contrasts may be used. If the assumptions of Definition 5.2.1 are not tenable, the consequences of violation and other concepts are discussed extensively for example in Kirk (1995, pp. 97–103).

## 5.3 Contrast among treatment group means

**Definition 5.3.1 (Linear combination of treatment group means).** *A linear combination of treatment group means $\mu_j$ is an expression of the form*

$$\psi = c_1\mu_1 + \cdots + c_s\mu_s = \sum_{j=1}^{s} c_j\mu_j,$$

*where the coefficients $c_j$ are known constants and $s$ is the number of treatments.*

**Remark.** In Section 5.2, the index $j$ runs from $A_1$ to $B_l$ and has $s = k + l$ values.

**Definition 5.3.2 (Linear contrast or comparison).** *A linear contrast or comparison among treatment group means is a linear combination of treatment group means for which*

1) *at least one coefficient is not equal to zero ($\exists j \in \mathcal{A} \cup \mathcal{B} \ : \ c_j \neq 0$) and*
2) *the coefficients sum to zero ($\sum_{i=1}^{s} c_i = 0$).*

**Remark.**

- Instead of treatment group means $\mu_j$ of the response, we can also use the treatment effects $\tau_j$ in Definition 5.3.2, since by condition 2) together with $\mu_j = \mu + \tau_j$, we obtain

$$\psi = \sum_{j=1}^{s} c_j\mu_j = \mu \sum_{j=1}^{s} c_j + \sum_{j=1}^{s} c_j\tau_j = \sum_{j=1}^{s} c_j\tau_j.$$

- The least-squares estimator of $\psi$ is

$$\hat{\psi} = \sum_{j=1}^{s} c_j \bar{Y}_{j\cdot} \ .$$

The variance of $\hat{\psi}$ is

$$\sigma^2_{\hat{\psi}} = \sum_{j=1}^{s} c_j^2 \mathrm{Var}[\bar{Y}_{j\cdot}] = \sigma^2_{\varepsilon} \sum_{j=1}^{s} \frac{c_j^2}{n_j},$$

which is estimated by

$$\hat{\sigma}^2_{\hat{\psi}} = \mathrm{MS}_{\mathrm{RES}} \sum_{j=1}^{s} \frac{c_j^2}{n_j}.$$

**Definition 5.3.3.**

1. *A linear contrast $\psi = \sum_{j=1}^{s} c_j \mu_j$ is called*
   a) *pairwise, if all of the coefficients $c_j$ except two are equal to zero. Otherwise, the contrast is called non-pairwise.*
   b) *normalised, if $\sum_{j=1}^{s} c_j^2/n_j = 1$.*
2. *Two linear contrasts $\psi_1 = \sum_{j=1}^{s} c_{1j}\mu_j$ and $\psi_2 = \sum_{j=1}^{s} c_{2j}\mu_j$ are called*
   a) *equivalent, if $c_{1j} = m c_{2j}$ for all $j = 1, \ldots, s$ with $m$ an arbitrary constant ($m \neq 0$).*
   b) *orthogonal, if $\sum_{j=1}^{s} c_{1j}c_{2j}/n_j = 0$. Otherwise, the contrasts are called non-orthogonal. Two contrasts $\psi_1$ and $\psi_2$ which are non-orthogonal are said to be correlated with correlation*

$$\rho_{12} = \frac{\sum_{j=1}^{s} \frac{c_{1j}c_{2j}}{n_j}}{\sqrt{\sum_{j=1}^{s} \frac{c_{1j}^2}{n_j} \sum_{j=1}^{s} \frac{c_{2j}^2}{n_j}}}.$$

3. *The contrasts of a set of linear contrast are called*

   *mutually orthogonal, if each contrast of the set is orthogonal to all other contrasts of the set.*

**Remark.**

- It is recommended to use normalised contrasts to avoid ambiguities due to the equivalent contrasts.
- If there are $s$ treatments, the maximum number of mutually orthogonal contrasts is equal to $s - 1$.

**Definition 5.3.4.** *Let $s$ be the number of treatments in model* (5.1)*. Then a set of $s - 1$ mutually orthogonal contrasts is called a complete orthogonal set.*

**Remark.** There exists an infinite number of complete orthogonal sets. The contrasts of two complete orthogonal sets need not necessarily be orthogonal. Furthermore, all other contrasts can be expressed as a linear combination of the mutually orthogonal contrasts of a complete orthogonal set.

### Sum of squares for a contrast

The variation due to a contrast can be defined as a component of $\mathrm{SS}_{\mathrm{BG}}$. The sum of squares for a contrast $\psi$ among treatment effects is denoted by $\mathrm{SS}_{\psi}$ and is computed as

$$\mathrm{SS}_{\psi} = \frac{\hat{\psi}^2}{\sum_{j=1}^{s} \frac{c_j^2}{n_j}}.$$

Since the sum of squares for a contrast has only one degree of freedom, it is equal to the mean squares for this contrast $\mathrm{MS}_{\psi}$.

In general, the sum of squares between groups $\mathrm{SS}_{\mathrm{BG}}$ can be totally decomposed with a complete orthogonal set of contrasts $\psi_1, \ldots, \psi_{s-1}$, i.e.

$$\mathrm{SS}_{\mathrm{BG}} = \mathrm{SS}_{\psi_1} + \mathrm{SS}_{\psi_2} + \cdots + \mathrm{SS}_{\psi_{s-1}} \ .$$

This holds for all complete orthogonal sets of contrasts. Since the sum of squares between groups has $s-1$ degrees of freedom and the sum of squares for a contrast has one degree of freedom, each degree of freedom of $\mathrm{SS}_{\mathrm{BG}}$ may be associated with one contrast of a complete orthogonal set. Using different complete sets of orthogonal contrasts, $\mathrm{SS}_{\mathrm{BG}}$ is partitioned differently. It is possible to construct a contrast $\psi_{\max}$ such that $\mathrm{SS}_{\mathrm{BG}} = \mathrm{SS}_{\psi_{\max}}$. For equal sample sizes a construction for $\psi_{\max}$ can be found for example in Winer et al. (1991, pp. 149-151).

### Hypotheses, a priori and a posteriori contrasts

For each contrast $\psi$ there is a null hypothesis

$$H_{\psi} : \psi = \sum_{j=1}^{s} c_j \mu_j = 0 \tag{5.6}$$

associated with it. The alternative hypothesis can be formulated one-sided or two-sided.

In planning a clinical trial, a researcher has a specific set of contrasts in mind, the corresponding hypotheses of which he wants to test (e.g. differences in treatment means). With regard to inferences on contrasts among treatment means, we have to distinguish whether the contrasts are a priori or a posteriori. A priori or planned contrasts are defined before running the clinical trial. These contrast are usually related to the structure of the data obtained. A posteriori or post hoc contrasts are derived from the structure of the outcome after the clinical trial was run.

To test the hypothesis (5.6) for an a priori contrast, we can use one of two following test statistics. First, we concentrate on a two-sided alternative hypotheses and define an $F_{\psi}$-statistic by following the considerations of the omnibus hypothesis

$$F_{\psi} = \frac{\mathrm{MS}_{\psi}}{\mathrm{MS}_{\mathrm{RES}}} \ . \tag{5.7}$$

Under the null hypothesis, and if the assumptions of Definition 5.2.1 are met, the statistic

$F_\psi$ is $F$-distributed with $\mathrm{df}_\psi = 1$ and $\mathrm{df}_{\mathrm{RES}} = N - s$ degrees of freedom. The decision rule is to reject the null hypothesis if the value of the statistic $F_\psi$ is larger than $F_{1-\alpha}(\mathrm{df}_\psi, \mathrm{df}_{\mathrm{RES}})$, otherwise we do not reject $H_\psi$. The $t_\psi$-statistic with

$$t_\psi = \frac{\hat{\psi}}{\sqrt{\hat{\sigma}^2_{\hat{\psi}}}} = \frac{\sum_{j=1}^{s} c_j \bar{Y}_{j\cdot}}{\sqrt{\mathrm{MS}_{\mathrm{RES}} \sum_{j=1}^{s} \frac{c_j^2}{n_j}}} \tag{5.8}$$

may also be used to test the hypothesis, since

$$t^2_\psi = \frac{\hat{\psi}^2}{\mathrm{MS}_{\mathrm{RES}} \sum_{j=1}^{s} \frac{c_j^2}{n_j}} = \frac{\mathrm{MS}_\psi}{\mathrm{MS}_{\mathrm{RES}}} = F_\psi.$$

Under the null hypothesis, and if the assumptions of Definition 5.2.1 are met, $t_\psi$ follows a Student's $t$-distribution with $\mathrm{df}_{\mathrm{RES}} = N - s$ degrees of freedom. The decision rule is to reject the null hypothesis if the value of $|t_\psi|$ is larger than the $1 - \alpha/2$ quantile of the $t$-distribution with $\mathrm{df}_{\mathrm{RES}}$ degrees of freedom $t_{1-\alpha/2}(\mathrm{df}_{\mathrm{res}})$. The equation

$$t^2_{1-\alpha/2}(\mathrm{df}_{\mathrm{RES}}) = F_{1-\alpha}(1, \mathrm{df}_{\mathrm{RES}}).$$

holds for the quantiles of the $t$- and the $F$-distribution.

Second, for the one-sided case, the decision rules are changed to reject the null hypothesis if the value of the statistic $t_\psi$ is larger than $t_{1-\alpha}(\mathrm{df}_{\mathrm{RES}})$. The equivalent $F$-test would reject the null hypothesis if the value of the statistic $F_\psi$ is larger than $F_{1-2\alpha}(1, \mathrm{df}_{\mathrm{RES}})$.

### Multiple testing

To test only one a priori contrast, the probability of a type I error is equal to the level of significance $\alpha$. If we consider two or more contrasts, the situation is more complex and depends on whether the contrasts are orthogonal or not and whether they are a priori or a posteriori. When testing multiple hypotheses simultaneously, the probability of a type I error is larger than for testing one single hypothesis. If we consider $Z$ independent tests, each test can be evaluated on its own and its probability of not making a type I error is $1 - \alpha$. For independent tests, the probability of not making one ore more type I error is the product of the single probabilities $(1 - \alpha)^Z$. Consequently the

$$\text{probabily of making at least one type I error} = 1 - (1 - \alpha)^Z > \alpha$$

for $Z > 1$. For $Z$ dependent tests, the probability of making one or more type I errors is less than or equal to $1 - (1 - \alpha)^Z$. Obviously, if the number of tests increases, the probability of one or more false positive decisions increases also. The multiple tests of contrasts are not independent even if the contrasts are orthogonal, since the error variance in the denominators of the corresponding $t$-tests is the same.

In most cases, the research strategy is to control the type I error at $\alpha$ for the set of contrasts that are tested. Therefore, an adjustment can be performed by computing a reduced significance level for each hypothesis. To control the type I error at $\alpha$ for a set or family of contrasts, different type I error rates are defined, e.g. the per-contrast error rate, the familywise error rate and the per-family error rate. For more information about the different error rates and their relationship see for example Kirk (1995, pp. 119–122) or Dmitrienko et al. (2009, pp. 36–39)). Since we are interested in orthogonal and non-

orthogonal as well as pairwise and non-pairwise contrasts, we concentrate on controlling the familywise error rate, which is the probability of making at least one type I error in the family.

Let $Z \geq 1$ denote the number of null hypotheses $H_{\psi_1}, \ldots, H_{\psi_Z}$ to be tested with alternative hypotheses $K_{\psi_1}, \ldots, K_{\psi_Z}$. Each of the tests $H_{\psi_i}$, $i = 1, \ldots, Z$, is associated with a given contrast $\psi_i = \sum_{j=1}^{s} c_{ij}\mu_j$ of interest. Let $t_{\psi_1}, \ldots, t_{\psi_Z}$ denote the corresponding test statistics for each contrast. In the two-sided test problems the absolute values of the individual test statistics are taken and larger values of $t_{\psi_i}$ favour the rejection of $H_{\psi_i}$. Then one natural approach for the multiple contrast test uses the max-$t$ test statistic with

$$t_{\psi_{\max}} = \max\{t_{\psi_1}, \ldots, t_{\psi_Z}\}.$$

Under the assumption from Definition 5.2.1 of model (5.1), it can be shown that under the global null hypothesis $\mathcal{H} = \cap_{i \in I} H_{\psi_i}$, $I = \{1, \ldots, Z\}$, the joint distribution of $t_{\psi_1}, \ldots, t_{\psi_Z}$ is a multivariate $t$-distribution with correlation matrix $\mathbf{R} = (\rho_{ij})$, where $\rho_{ij}$ is the correlation between the contrasts $\psi_i$ and $\psi_j$. The test rejects $\mathcal{H}$ if $t_{\psi_{\max}} > q$, where $q$ denotes the upper $\alpha$ critical point of this distribution. For computing the multivariate $t$ probabilities, see Genz and Bretz (2002, 2009). For testing all contrasts, we use a step-down algorithm based on max-$t$ tests under the free combination condition. This means that for any subset, the simultaneous truth of $H_{\psi_i}$ and falsehood of the remaining hypotheses is a plausible event. The presented algorithm originates from Bretz et al. (2010).

**Step** 1: Let $I_1 = \{1, \ldots, Z\}$. The test of the global null hypothesis $\mathcal{H}_I = \cap_{i \in I} H_{\psi_i}$ with a suitable max-$t$ test results in a p-value $p_I$.

- If $p_I \leq \alpha$, then determine $i_1 := \arg\max_{i \in I} t_{\psi_i}$ and reject $H_{\psi_{i_1}}$ with adjusted p-value $q_{i_1} = p_I$. Proceed to the next step.
- Otherwise stop.

**Step** 2: Let $I_2 = I_1 \setminus \{i_1\}$. The test $\mathcal{H}_{I_2} = \cap_{i \in I_2} H_{\psi_i}$ with a suitable max-$t$ test results in a p-value $p_{I_2}$.

- If $p_{I_2} \leq \alpha$, then determine $i_2 := \arg\max_{i \in I_2} t_{\psi_i}$ and reject $H_{\psi_{i_2}}$ with adjusted p-value $q_{i_2} = \max\{q_{i_1}, p_{I_2}\}$. Proceed to the next step.
- Otherwise stop.

$\vdots$

**Step** $j$: Let $I_j = I_{j-1} \setminus \{i_{j-1}\}$. The test $\mathcal{H}_{I_j} = \cap_{i \in I_j} H_{\psi_i}$ with a suitable max-$t$ test results in a p-value $p_{I_j}$.

- If $p_{I_j} \leq \alpha$, then determine $i_j := \arg\max_{i \in I_j} t_{\psi_i}$ and reject $H_{\psi_{i_j}}$ with adjusted p-value $q_{i_j} = \max\{q_{i_{j-1}}, p_{I_j}\}$. Proceed to the next step.
- Otherwise stop.

$\vdots$

**Step** $Z$: Let $I_Z = I_{Z-1} \setminus \{i_{Z-1}\} = \{i_Z\}$. The test $\mathcal{H}_{I_Z} = \cap_{i \in I_Z} H_{\psi_i}$ with a suitable max-$t$ test results in a p-value $p_{I_Z}$.

- If $p_{I_Z} \leq \alpha$, then determine $i_Z := \arg\max_{i \in I_Z} t_{\psi_i}$ and reject $H_{\psi_{i_Z}}$ with adjusted p-value $q_{i_Z} = \max\{q_{i_{Z-1}}, p_{I_Z}\}$. Procedure stops.

Another popular procedure for testing any of the possible contrast among effects is the $S$-method which has been developed by Scheffé and is now better known as Scheffé's test. This approach uses a confidence interval on the maximum normalized contrast. The idea is the following: if this confidence interval holds for the maximum contrast, it will hold simultaneously for all contrasts. However, for all contrasts except the maximum contrast, the confidence interval is conservative.

**Theorem 5.3.5 (Scheffé (1959))**. *The probability that the values of all contrasts simultaneously satisfy the inequalities*

$$\hat{\psi} - S\hat{\sigma}_{\hat{\psi}} \leq \psi \leq \hat{\psi} + S\hat{\sigma}_{\hat{\psi}}$$

*is* $1-\alpha$*, where the constant* $S$ *is given by*

$$S^2 := (s-1)F_{1-\alpha}(s-1,N-s).$$

**Remark.**

- Scheffé's test is robust with respect to violations of the assumptions of Definition 5.2.1 and it does not require equal sample sizes (cf. Winer et al. (1991, pp. 191–197)). Scheffé's test can be also used for an a posteriori test, which means all contrasts that appear interesting from an inspection of the data can be tested under control of the type I error. However, this test procedure is not as powerful as other ones (cf. Kirk (1995, pp. 126–127, 154–155)).
- If the $F$-test of the omnibus null hypothesis is significant, at least one contrast among the treatment effects is not equal to zero. However, it could happen that this contrast is not of any practical interest. For more information about the relationship of the Scheffé's test to the $F$-test if the omnibus hypothesis see Scheffé (1959, pp. 70–72) or Winer et al. (1991, pp. 191–195).
- Computing the confidence interval is equivalent to computing the $F$-statistic used for individual contrasts $F_\psi = \mathrm{MS}_\psi/\mathrm{MS}_{\mathrm{RES}}$ and rejecting the null hypothesis (5.6) if the value of the test statistic is larger than $S^2 = (s-1)F_{1-\alpha}(s-1,N-s)$.

## 5.4 Contrasts among treatment group means in a $\mathrm{POR}_{k,l}$ design

### 5.4.1 Strategy comparison contrast

The contrasts which are of interest in the context of a patient-oriented randomisation design are presented in this section. Primarily, we are interested in a contrast comparing the two different strategies. Since the coefficients of a contrast have to be known constants and we assume that all treatments in each strategy are equally probable. We consider the linear combination

$$\begin{aligned}\psi &= \frac{1}{k}\mu_{A_1} + \cdots + \frac{1}{k}\mu_{A_k} - \frac{1}{l}\mu_{B_1} - \cdots - \frac{1}{l}\mu_{B_l} \\ &= \frac{1}{k}\sum_{i=1}^{k}\mu_{A_i} - \frac{1}{l}\sum_{j=1}^{l}\mu_{B_j}\end{aligned}$$

to compare both strategies. This linear combination is a contrast, since

$$\sum_{j=1}^{k+l} c_j = \sum_{j=1}^{k} \frac{1}{k} + \sum_{j=1}^{l} -\frac{1}{l} = 1 - 1 = 0.$$

**Definition 5.4.1 (Strategy comparison contrast)**. *Let $A_1, \ldots, A_k$ be treatments of strategy $\mathcal{A}$ and $B_1, \ldots, B_l$ be treatments of strategy $\mathcal{B}$. The linear contrast*

$$\psi_0 = \frac{1}{k}\mu_{A_1} + \cdots + \frac{1}{k}\mu_{A_k} - \frac{1}{l}\mu_{B_1} - \cdots - \frac{1}{l}\mu_{B_l} \tag{5.9}$$

*among treatment means of two strategies $\mathcal{A}$ and $\mathcal{B}$ is called strategy comparison contrast between $\mathcal{A}$ and $\mathcal{B}$.*

**Remark.**

- If we wish to test only the strategy comparison contrast, we can use the presented $t$-test (see Equation (5.8)) or the $F$-test (see Equation (5.7)).

- For the purpose of strategy comparison, it might be desirable for the contrast to account for possible imbalances in the sample size of the treatment groups. This would lead to the coefficients

$$c_j = n_j / \sum_{i \in \mathcal{A}} n_i \quad \text{for} \quad j \in \mathcal{A} \tag{5.10}$$

and

$$c_j = -n_j / \sum_{i \in \mathcal{B}} n_i \quad \text{for} \quad j \in \mathcal{B}. \tag{5.11}$$

for the contrast. However, the actual sample sizes observed in a study might differ from the pre-planned sample sizes and are in general unknown prior to the conduct of the study. Therefore, the contrast with the coefficients from (5.10) and (5.11) is not a priori and can thereby not be tested with the step-down procedure outlined in Section 5.3.

Nevertheless, it is possible to formulate an a priori contrast that accounts for the imbalances when we use strategy as factor in contrast to treatment as was done here, the estimated strategy comparison contrast

$$\hat{\psi} = \hat{\mu}_{\mathcal{A}} - \hat{\mu}_{\mathcal{B}}$$

(where $\hat{\mu}_{\mathcal{A}} = 1/n_{\mathcal{A}} \sum_{j \in \mathcal{A}} \sum_{i=1}^{n_j} y_{ji}$ and $\hat{\mu}_{\mathcal{B}} = 1/n_{\mathcal{B}} \sum_{j \in \mathcal{B}} \sum_{i=1}^{n_j} y_{ji}$ are the mean responses in the two strategies and $n_{\mathcal{A}}$ and $n_{\mathcal{B}}$ are the sample sizes in both strategies) is equivalent to the estimated contrast with coefficients from (5.10) and (5.11) in the model with treatment as factor, since

$$\begin{aligned} \hat{\psi} &= \sum_{j \in \mathcal{A} \cup \mathcal{B}} c_j \hat{\mu}_j \\ &= \sum_{j \in \mathcal{A}} c_j \ \hat{\mu}_j + \sum_{j \in \mathcal{B}} c_j \ \hat{\mu}_j \end{aligned}$$

$$
\begin{aligned}
&= \underbrace{\frac{\sum_{j\in\mathcal{A}} n_j \hat{\mu}_j}{\sum_{i\in\mathcal{A}} n_i}}_{=n_{\mathcal{A}}} + \underbrace{\frac{\sum_{j\in\mathcal{B}} -n_j\ \hat{\mu}_j}{\sum_{i\in\mathcal{B}} n_i}}_{=n_{\mathcal{B}}} \\
&= \frac{\sum_{j\in\mathcal{A}} n_j \bar{Y}_{j\cdot}}{n_{\mathcal{A}}} - \frac{\sum_{j\in\mathcal{B}} n_j\ \bar{Y}_{j\cdot}}{n_{\mathcal{B}}} \\
&= \frac{\sum_{j\in\mathcal{A}} \sum_{i=1}^{n_j} Y_{ji}}{n_{\mathcal{A}}} - \frac{\sum_{j\in\mathcal{B}} \sum_{i=1}^{n_j} Y_{ji}}{n_{\mathcal{B}}} \\
&= \hat{\mu}_{\mathcal{A}} - \hat{\mu}_{\mathcal{B}}.
\end{aligned}
$$

### 5.4.2 Patient-oriented decision versus randomisation contrast

In addition to the main hypothesis described by the strategy comparison contrast (Definition 5.4.1) above, we are also interested in other questions concerning the patient-oriented decision, e.g. whether it is possible to prove that the patient-oriented choice results in a more effective treatment as opposed to pure randomisation. In the CUtLASS design, it is not possible to answer this question because there is no randomised reference population. To see how the effect of patient-oriented treatment decisions can be investigated in a $\mathrm{POR}_{k,l}$ design and which further information is needed, we consider the following example.

**Example.** For our example $\mathrm{POR}_{2,2}$, we consider the two-pair combinations of Table 5.1 and separate the treatments of both strategies according to only randomised choice treated patients and patient-oriented choice treated patients. Thereby the superscript $R$ following the treatments indicates that the patients received the treatment due to randomisation's reasons. Similarly, the superscript $P$ indicates that the patients received the treatment not only due to randomisation, but due to a patient-oriented decision of the physician. The information whether the patient received the treatments of a two-pair combination due to patient-oriented decision or only due to randomisation reasons is marked with 'X'.

| No. of two-pair combination | $\mathcal{TPC}_{2,2}$ | | Randomised treatmens | | | | Patient-oriented treatmens | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Pair 1 | Pair 2 | $A_1^R$ | $A_2^R$ | $B_1^R$ | $B_2^R$ | $A_1^P$ | $A_2^P$ | $B_1^P$ | $B_2^P$ |
| Clear decision between $A_1 \leftrightarrow A_2$ | | | | | | | | | | |
| 2 | $(A_1,B_1)$ | $(A_2,B_1)$ | X | X | X | | X | X | | |
| 5 | $(A_1,B_2)$ | $(A_2,B_2)$ | X | X | | X | X | X | | |
| Clear decision between $B_1 \leftrightarrow B_2$ | | | | | | | | | | |
| 1 | $(A_1,B_1)$ | $(A_1,B_2)$ | X | | X | X | | | X | X |
| 6 | $(A_2,B_1)$ | $(A_2,B_2)$ | | X | X | X | | | X | X |
| No clear decision | | | | | | | | | | |
| 3 | $(A_1,B_1)$ | $(A_2,B_2)$ | X | X | X | X | X | X | X | X |
| 4 | $(A_1,B_2)$ | $(A_2,B_1)$ | X | X | X | X | X | X | X | X |

Table 5.1: Two-pair combinations of the $\mathrm{POR}_{2,2}$ design. Treatments separated according to patients receiving this treatment due to randomisation ('R') or due to patient-oriented choice ('P') are marked with 'X'.

As we described before, the physician selected one pair out of a randomly chosen two-pair combination. In four out of the six two-pair combinations, we have one identical pair. If the patient is randomised to the strategy with the identical pair in both two-pair combinations, the physician's decision had no influence on the treatment received. If the randomisation in step 2 allocates the other strategy, the treatment follows the physician's decision. Hence in two-pair combinations with a clear patient-oriented decision, we can distinguish between a merely randomised patient and a randomised patient with a patient-oriented decision. This classification is marked with a black 'X' in Table 5.1. For this classification in TPCs 2, 5, 1 and 6, we assume a conscious decision of the physician between the two treatments of the mixed pair. However, it could also happen that the physician favours no treatment of the mixed pair for a certain patient and selects one of the random pairs at random. Then the patients can be classified as treated with a treatment due to randomisation's reasons. This special case is marked with a red 'X' in Table 5.1.

In the mixed combinations without clear decision, we can not make this classification directly. The physician may have chosen one of the pairs on the basis of one preferred treatment of this pair and not of both. If the randomisation in step 2 allocates the patient to the preferred treatment, the treatment would be classified as patient-oriented treatment. However, in case that the randomisation in step 2 allocates the patient to the other treatment, the treatment would be classified as randomised treatment. Hence we see that we need additional information about the preferred treatment of the physician in each strategy of this two-pair combination to classify the treatments. Either this information is available for each patient and we can take this into account, or the information is missing for some patients. In this case, we have two opportunities. Either we ignore this information by disregarding all patients without clear decision, or we take this information into account under the assumption that the missing information is missing at random. That means we use the data of all patients where we have the information whether the allocation was purely random or due to a patient-oriented decision (complete case analysis). In the following part of this thesis, we assume that we have all required information available and we can classify each patient to one of the two groups ($P$ and $R$).

Due to the classification of the treatments into randomised and patient-oriented, we see that our model 5.2.1 is no longer sufficient.

**Definition 5.4.2.** *The set of all patient-oriented choice treated patients is called patient-oriented group and the set of all random choice treated patients is called random group.*

**Notation.** The superscript $R$ following the treatments $A_1, \ldots, A_k, B_1, \ldots, B_l$ indicates that the patients received the treatment due to randomisation's reasons. Similarly, the superscript $P$ indicates that the patients received the treatment not only due to randomisation, but due to a patient-oriented decision of the physician. This leads to the following notations

- $\mathcal{A}^R = \{A_1^R, \ldots, A_k^R\}$ and $\mathcal{A}^P = \{A_1^P, \ldots, A_k^P\}$
- $\mathcal{B}^R = \{B_1^R, \ldots, B_l^R\}$ and $\mathcal{B}^P = \{B_1^P, \ldots, B_l^P\}$.

**Definition 5.4.3 (Extended unbalanced one-way classification with fixed-effects for a $\mathrm{POR}_{k,l}$ design).** *The model equation for an extended unbalanced one-way classification with fixed-effects for a* $\mathrm{POR}_{k,l}$ *design is*

$$Y_{ji} = \mu_j + \varepsilon_{ji} \qquad \begin{array}{l} \text{for} \quad i = 1, \ldots, n_j \\ \text{and} \quad j \in \mathcal{A}^R \cup \mathcal{A}^P \cup \mathcal{B}^R \cup \mathcal{B}^P \end{array} \tag{5.12}$$

*where*

*for $j \in \mathcal{A}^R \cup \mathcal{B}^R$, $\mu_j$ is the treatment group mean of the randomised group.*

*for $j \in \mathcal{A}^P \cup \mathcal{B}^P$, $\mu_j$ is the treatment group mean of the patient-oriented group.*

*For the fixed-effects model assumption, the model Equation (5.12) contains all the sources of variation that affect $Y_{ji}$. The treatment group means $\mu_j$ for the $j$th factor level for $j \in \mathcal{A}^R \cup \mathcal{A}^P \cup \mathcal{B}^R \cup \mathcal{B}^P$ are constant. The only source of variation is the error $\varepsilon_{ji}$. We assume that $\varepsilon_{ji} \overset{\text{i.i.d.}}{\sim} \mathcal{N}(0,\sigma_\varepsilon^2)$. $\sigma_\varepsilon^2$ is referred to as error variance.*

**Remark.**

1. Model (5.12) can equivalently be parametrised by

$$Y_{ji} = \mu_j^R + \mathbb{1}_{\{\Delta_i = 1\}}\delta_j + \varepsilon_{ji} \tag{5.13}$$

with

$$\begin{aligned} j &= A_1, \ldots, A_k, B_1, \ldots, B_l \\ i &= 1, \ldots, n_j \\ \Delta_i &= \begin{cases} 0, & \text{if patient } i \text{ is in the random group.} \\ 1, & \text{if patient } i \text{ is in patient-oriented group.} \end{cases} \end{aligned}$$

where

$\mu_j^R$ is the treatment group mean of patients in the random group treated with treatment $j$.

$\Delta_i$ is an indicator variable indicating whether the patient is in the random or patient-oriented group.

$\delta_j$ is the treatment group mean difference between the random or patient-oriented group for the $j$th treatment.

Since the two models (5.12) and (5.13) are equivalent, the same questions can be answered. In the second model, the effect of patient-oriented decisions is directly modelled by the $\delta_j$. However, in the first model, the contrasts which are of major interest in this thesis are easier to formulate, which is why we chose that parametrisation.

2. Model (5.12) has twice the number of levels compared with model (5.1). The degrees of freedom of the sum of squares within groups decreases to $\mathrm{df}_{\mathrm{RES}} = N - 2(k+l)$. The degrees of freedom of the sum of squares between groups increases to $\mathrm{df}_{\mathrm{BG}} = 2(k+l) - 1$.

3. The strategy comparison contrast from Definition 5.4.1 can also be formulated with model (5.12) as

$$\psi_0 = \frac{1}{k}\sum_{i=1}^{k}\frac{1}{2}\left(\mu_{A_i^R} + \mu_{A_i^P}\right) - \frac{1}{l}\sum_{j=1}^{l}\frac{1}{2}\left(\mu_{B_j^R} + \mu_{B_j^P}\right).$$

However, the test statistics (5.7) and (5.8) change slightly due to the number of parameters to estimate and the associated change in the sum of squares within groups and their degrees of freedom.

**Definition 5.4.4 (Patient-oriented decision versus randomised contrasts)**. *Let* (5.12) *be the underlying model. Then the following contrasts and their corresponding contrast tests are of interest.*

1. *The contrast*

$$\psi_1 = \sum_{i=1}^{k} \mu_{A_i^R} + \sum_{j=1}^{l} \mu_{B_j^R} - \sum_{i=1}^{k} \mu_{A_i^P} - \sum_{j=1}^{l} \mu_{B_j^P}$$

*compares the treatment group means of the random group and the patient-oriented group.*

2. *The contrasts*

$$\psi_2 = \sum_{i=1}^{k} \mu_{A_i^R} - \sum_{i=1}^{k} \mu_{A_i^P} \qquad \psi_3 = \sum_{j=1}^{l} \mu_{B_j^R} - \sum_{j=1}^{l} \mu_{B_j^P}$$

*compare the treatment group means of the random group and the patient-oriented group by strategy.*

3. *The contrasts*

$$\begin{aligned} \psi_{3+i} &= \mu_{A_i^R} - \mu_{A_i^P} && \text{for} \quad i = 1, \ldots, k, \\ \psi_{3+k+j} &= \mu_{B_j^R} - \mu_{B_j^P} && \text{for} \quad j = 1, \ldots, l. \end{aligned}$$

*compare the treatment group means of the random group and the patient-oriented group by treatment.*

4. *The contrast*

$$\psi_{4+k+l} = \sum_{i=1}^{k} \frac{1}{k} \mu_{A_i^R} - \sum_{j=1}^{l} \frac{1}{l} \mu_{B_j^R}$$

*compares the treatment group means of the random group between both strategies and the contrast*

$$\psi_{5+k+l} = \sum_{i=1}^{k} \frac{1}{k} \mu_{A_i^P} - \sum_{j=1}^{l} \frac{1}{l} \mu_{B_j^P}$$

*compares the treatment group means of the patient-oriented group between both strategies.*

**Remark.** In total, there are $6+k+l$ contrasts of interest. Each contrast considers an other aspect of the $\text{POR}_{k,l}$ designs. $\psi_0$, $\psi_{4+k+l}$ and $\psi_{5+k+l}$ compare the differences between the strategies. $\psi_0$ describes our main contrast comparing the two different strategies. Due to the contrasts $\psi_{4+k+l}$ and $\psi_{5+k+l}$, it is possible to prove the assumption of heterogeneous patient-drug-interaction. The scenario where the $\text{POR}_{k,l}$ design is most advantageous (compared to other randomisation schemes), is one where there are differences in treatment group means of the patient-oriented group between both strategies and no differences in the treatment group means of the random group between both strategies. That means that the heterogeneity of patient-drug-interaction of the responders and non-responders may cancel each other out in the block design as we have seen in our example in the introductory section. The effect in the treatment means between the strategy in the patient-oriented group can only be seen because of the physician's decision.

Although the physician's decision may result in a higher treatment group mean, it could happen that the higher group mean occurs in both strategies equally strong, or that not all decisions in all treatments lead to higher group mean. Therefore, the contrasts $\psi_1$, $\psi_2$, $\psi_3$, $\psi_{3+1}, \ldots, \psi_{3+k+l}$ are of interest. These contrasts compare the treatment group means between patient-oriented and random group in each treatment, each strategy and overall and not the effects between the treatments of different strategies.

The $k+l$ contrasts $\psi_{3+1}, \ldots, \psi_{3+k+l}$ are pairwise and mutually orthogonal. In addition they are all orthogonal to the contrast $\psi_0$. The set of contrasts $\boldsymbol{\psi} = \{\psi_0, \psi_{3+1}, \ldots, \psi_{3+k+l}\}$ forms one possible base for all contrasts which we are interested in, since all other contrasts $\psi_1$, $\psi_2$, $\psi_3$, $\psi_{4+k+l}$ and $\psi_{5+k+l}$ can be derived via linear combinations from elements of $\boldsymbol{\psi}$:

$$\begin{aligned}
\psi_1 &= \psi_{3+1} + \cdots + \psi_{3+k+l},\\
\psi_2 &= \psi_{3+1} + \cdots + \psi_{3+l},\\
\psi_3 &= \psi_{3+l+1} + \cdots + \psi_{3+l+k}\\
\psi_{4+k+l} &= \psi_0 + \frac{1}{2}\psi_{3+1} + \cdots + \frac{1}{2}\psi_{3+l} - \frac{1}{2}\psi_{3+l+1} - \cdots - \frac{1}{2}\psi_{3+l+k},\\
\psi_{5+k+l} &= \psi_0 - \frac{1}{2}\psi_{3+1} - \cdots - \frac{1}{2}\psi_{3+l} + \frac{1}{2}\psi_{3+l+1} + \cdots + \frac{1}{2}\psi_{3+l+k}.
\end{aligned}$$

Other sets of contrasts are also mutually orthogonal, e.g. $\{\psi_0, \psi_2, \psi_3\}$, $\{\psi_1, \psi_{4+k+l}, \psi_{5+k+l}\}$, $\{\psi_2, \psi_{3+l+1}, \ldots, \psi_{3+l+k}\}$ and $\{\psi_3, \psi_{3+1}, \ldots, \psi_{3+1+l}\}$. However, the dimension of $\boldsymbol{\psi}$ is largest with $k+l+1$. The dimension of a set of mutually orthogonal contrasts of model (5.12) is at most $2(k+l)-1$. Therefore, the remaining $k+l-2$ dimensions are not reached with the contrasts of interest.

Depending on the particular clinical trial, some of the contrasts may be more important than others.

## 5.5 Sample size calculation

In this section, we concentrate on the determination of the total sample size needed to test the strategy comparison contrast (5.9). We will further investigate how the allocation of sample sizes in each treatment influences the total sample size. To test the corresponding null hypothesis (5.6),

$$H_{\psi_0} : \psi_0 = \frac{1}{k}\mu_{A_1} + \cdots + \frac{1}{k}\mu_{A_k} - \frac{1}{l}\mu_{B_1} - \cdots - \frac{1}{l}\mu_{B_l} = 0,$$

we use the $t_{\psi_0}$-statistic with

$$t_{\psi_0} = \frac{\hat{\psi}_0}{\sqrt{\hat{\sigma}^2_{\hat{\psi}_0}}} = \frac{\sum_{j\in\mathcal{A}\cup\mathcal{B}} c_j \bar{Y}_{j\cdot}}{\sqrt{\hat{\sigma}^2_\varepsilon \sum_{j\in\mathcal{A}\cup\mathcal{B}} \frac{c_j^2}{n_j}}}$$

(cf. O'Brien and Muller (1993, pp. 297–344)). Under the null hypothesis, and if the assumption of Definition 5.2.1 are met, $t_{\psi_0}$ follows a Student's $t$-distribution with $\mathrm{df}_{\mathrm{RES}} = N - (k+l)$ degrees of freedom. Under the alternative hypothesis $K_{\psi_0}$, i.e if $\Delta = \psi_0 \neq 0$, and if $\hat{\psi}_0$ is distributed as $\mathcal{N}(\Delta, \sigma^2_\varepsilon \sum_{j=1}^s c_j^2/n_j)$, we have

$$\begin{aligned} t_{\psi_0} &= \frac{\hat{\psi}_0 - \Delta}{\sqrt{\hat{\sigma}^2_\varepsilon \sum_{j\in\mathcal{A}\cup\mathcal{B}} \frac{c_j^2}{n_j}}} + \frac{\Delta}{\sqrt{\sigma^2_\varepsilon \sum_{j\in\mathcal{A}\cup\mathcal{B}} \frac{c_j^2}{n_j}}} \sqrt{\frac{\sigma^2_\varepsilon}{\hat{\sigma}^2_\varepsilon}} \\ &= t'_{\psi_0} + \delta \sqrt{\frac{\sigma^2_\varepsilon}{\hat{\sigma}^2_\varepsilon}}, \end{aligned}$$

where

$$\delta = \frac{\Delta}{\sqrt{\sigma^2_\varepsilon \sum_{j\in\mathcal{A}\cup\mathcal{B}} \frac{c_j^2}{n_j}}} \tag{5.14}$$

and $t'_{\psi_0}$ follows a central $t$-distribution with $N-(k+l)$ degrees of freedom. Consequently, $t_{\psi_0}$ follows a noncentral $t$-distribution with $\mathrm{df}_{\mathrm{RES}} = N-(k+l)$ degrees of freedom and noncentrality parameter $\delta$. We denote this distribution by $t(\mathrm{df}_{\mathrm{RES}},\, \delta)$. The noncentral $t$-distribution permits us to calculate the power of the test with respect to the alternative $K_{\psi_0}$. In the two-sided test, the power is

$$\begin{aligned} &\mathbb{P}\left(|t(\mathrm{df}_{\mathrm{RES}},\, \delta)| \geq t_{1-\alpha/2}(\mathrm{df},\, 0)\right) \\ &= \mathbb{P}\left(t(\mathrm{df}_{\mathrm{RES}},\, \delta) \geq t_{1-\alpha/2}(\mathrm{df},\, 0)\right) + \mathbb{P}\left(-t(\mathrm{df}_{\mathrm{RES}},\, \delta) \geq t_{1-\alpha/2}(\mathrm{df}_{\mathrm{RES}},\, 0)\right) \\ &= 1 - \mathbb{P}\left(t(\mathrm{df}_{\mathrm{RES}},\, \delta) \leq t_{1-\alpha/2}(\mathrm{df},\, 0)\right) + \mathbb{P}\big(t(\mathrm{df}_{\mathrm{RES}},\, \delta) \leq \underbrace{-t_{1-\alpha/2}(\mathrm{df}_{\mathrm{RES}},\, 0)}_{=t_{\alpha/2}(\mathrm{df}_{\mathrm{RES}},\, 0)}\big) \\ &= 1 - \mathbb{P}\left(t(\mathrm{df}_{\mathrm{RES}},\, \delta) \leq t_{1-\alpha/2}(\mathrm{df}_{\mathrm{RES}},\, 0)\right) + \mathbb{P}\big(t(\mathrm{df}_{\mathrm{RES}},\, \delta) \leq t_{\alpha/2}(\mathrm{df}_{\mathrm{RES}},\, 0)\big) \end{aligned} \tag{5.15}$$

and for the one-sided test,

$$\begin{aligned} &\mathbb{P}\big(t(\mathrm{df}_{\mathrm{RES}},\, \delta) \geq t_{1-\alpha}(\mathrm{df},\, 0)\big) \\ &= 1 - \mathbb{P}\big(t(\mathrm{df}_{\mathrm{RES}},\, \delta) \leq t_{1-\alpha}(\mathrm{df},\, 0)\big). \end{aligned} \tag{5.16}$$

Equation (5.14) shows that the noncentrality parameter $\delta$, which determines power, is a function of three parameters: the expected effect between both strategies $\Delta$, the common within-group standard deviation $\sqrt{\sigma^2_\varepsilon}$ and the treatments' sample sizes $n_{A_1}, \ldots, n_{A_k}, n_{B_1}, \ldots, n_{B_l}$. To estimate $\Delta$ and $\sqrt{\sigma^2_\varepsilon}$ we can use pilot data or data of previous studies. The allocation of the treatments' sample sizes can not be so easily determined, since these numbers depend on the physicians' decisions in the study (cf. Section 3). In order to enable an evaluation for the treatment sample sizes, we define the treatments'

sample sizes as proportion of the total sample size $N$, i.e.

$$n_j = w_j \cdot N \quad \text{for} \quad j \in \mathcal{A} \cup \mathcal{B},$$

with $\sum_{j \in \mathcal{A} \cup \mathcal{B}} w_j = 1$ and $\sum_{j \in \mathcal{A}} w_j = p_\Psi = 1/2$. With this notation, we obtain

$$\begin{aligned} \delta &= \frac{\Delta\sqrt{N}}{\sqrt{\sigma_\varepsilon^2 \sum_{j \in \mathcal{A} \cup \mathcal{B}} \frac{c_j^2}{w_j}}} \\ &= \frac{\Delta\sqrt{N}}{\sqrt{\sigma_\varepsilon^2}\sqrt{\eta}}, \end{aligned}$$

where

$$\eta := \sum_{j \in \mathcal{A} \cup \mathcal{B}} \frac{c_j^2}{w_j}.$$

The total sample size $N$ depends linearly on $\eta$. If $\eta$ becomes larger the total sample size $N$ increases. Which values we can assume for $\eta$ will be discussed in more detail below. It can easily be seen that in general, it it not possible to solve (5.15) or (5.16) for $N$. However, we demand that the minimum acceptable power should be larger than or equal to $1 - \beta$. To determine the required $N$, we have to insert different values for $N$ (in an increasing manner) in Equation (5.15) or (5.16) until the desired power is achieved.

For the two-sided case, the sample size consideration can also be made on the basis of the $F$-statistic (5.7), which under $K_{\psi_0}$ follows a noncentral $F$-distribution with 1 and $\mathrm{df}_{\mathrm{RES}}$ degrees of freedom and the noncentrality parameter $\lambda = \delta^2$ (cf. O'Brien and Muller (1993, pp. 297–344)).

Now that we know how to determine the total sample size, we consider different $\eta$s and the corresponding allocation of the treatments' sample sizes. The parameter $\eta$ depends only on the structure of the design. The proportions of the total sample size $w_j$ are included inversely in the calculation of $\eta$ with a weight $c_j^2$. This shows that imbalances in the strategy with more treatments weigh more heavily than in the other.

In the best case situation, all treatments in each strategy are balanced, i.e.

$$w_j = \frac{1}{2k} \quad \text{for} \quad j \in \mathcal{A} \quad \text{and} \quad w_j = \frac{1}{2l} \quad \text{for} \quad j \in \mathcal{B} \tag{5.17}$$

and we receive as minimum

$$\begin{aligned} \eta &= \sum_{j \in \mathcal{A}} \frac{c_j^2}{w_j} + \sum_{j \in \mathcal{B}} \frac{c_j^2}{w_j} \\ &= \sum_{j \in \mathcal{A}} \frac{2k}{k^2} + \sum_{j \in \mathcal{B}} \frac{2l}{l^2} \\ &= 2 + 2 = 4. \end{aligned}$$

To determine the maximum of $\eta$ is not so easy, since the treatments' sample sizes depended on each other.

However, the previous considerations of Chapters 2 and 3 are helpful to determine a lower bound for the maximum of $\eta$ in the $\mathrm{POR}_{k,l}$ design. To be able to describe the

different distributions, we introduce the following definition.

**Definition 5.5.1.** *Let $C_i$ and $C_{i'}$ be two different treatments of strategy $C$.*

1. *The treatment $C_{i'}$ is called preferred to $C_i$, if whenever $C_i$ and $C_{i'}$ were present in the mixed pair of one two-pair combination, the physician choose the random pair of the two-pair combination with treatment $C_{i'}$.*
2. *The treatments $C_{i'}$ and $C_i$ are called equally preferred, if the physicians chose the random pair of the two-pair combinations with $C_{i'}$ equally often as the random pair of the two-pair combinations with $C_i$.*

**Notation.** If $C_{i'}$ is preferred to $C_i$, we denote this with $C_{i'} \succ C_i$. If $C_{i'}$ and $C_i$ are equally preferred, we denote this with $C_{i'} \asymp C_i$.

**Remark.** If there is more than one relation given and both can be used in one two-pair combination, the first-mentioned should be prioritised, i.e. let $A_{i'} \succ A_i$ and $B_{i'} \succ B_i$ be given, then the decision of the physician prioritises the relationship in strategy $\mathcal{A}$ over that in strategy $\mathcal{B}$ in all two-pair combinations, where both decisions are possible. If there are more than two relations given, we continue this scheme.

To get an idea of sensible value for $w_j$, we look at the following example.

**Example.** To illustrate how the distribution of sample sizes in each treatment influences the total sample size, we return to the NeSSy study and look at the sample size calculation in the $\text{POR}_{2,3}$ design. It was required to test the two-sided hypothesis

$$H_0 : \psi_0 = \frac{1}{2}\mu_{A_1} + \frac{1}{2}\mu_{A_2} - \frac{1}{3}\mu_{B_1} - \frac{1}{3}\mu_{B_2} - \frac{1}{3}\mu_{B_3} = 0 \quad \text{vs.} \quad K_0 : \psi_0 \neq 0$$

with type I error $\alpha = 0.025$ and power $1 - \beta = 0.8$ at $\Delta = \pm 8$ when the observations have standard deviation $\sigma_\varepsilon = 20.28$. For the sample size calculation, a worst case scenario for treatment $A_1$ in strategy $\mathcal{A}$ was assumed, since treatment $A_1$ was not so popular in the past. Although the most side effects are caused by the high dosage and the treatment was used in the study with lower dosage, it was assumed that physicians often deselect treatment $A_1$. Therefore the proportion $w_{A_1}$ was assumed to take the minimum allocation probability 1/10 from Property 3.2.2, and the proportion $w_{A_2}$ then automatically takes the maximum allocation probability 4/10 from Property 3.3.3. Together, $w_{A_1}$ and $w_{A_2}$ sum up to $p_\Psi = 1/2$. The treatments' sample sizes of strategy $\mathcal{B}$ were assumed to be balanced, i.e. $w_{B_1} = w_{B_2} = w_{B_3} = 1/6$. With this assumption, we compute $\eta_1 = 5.125$ and a total sample size $N_1 = 316$.

In this example, we want to see how other assumptions on the allocation of treatments' sample sizes influence the total sample size. In Table 5.2, the proportions $w_{A_1}$, $w_{A_2}$, $w_{B_1}$, $w_{B_2}$ and $w_{B_3}$ as well as the corresponding $\eta$ and the total sample size for different scenarios of allocations of treatments' sample sizes are presented. Case 0 describes the balanced scenario, where the smallest total sample size was computed. Case 1 complies with the assumption of the NeSSy study, where it was assumed that treatment $A_1$ is always deselected when possible. Case 2 describes the distribution of the treatments' sample sizes, when additionally to the case 1, the treatments in strategy $\mathcal{B}$ are as unbalanced as possible. Case 3 assumes that treatment $B_1$ is always deselected when possible and all other treatments are balanced. In addition, case 4 also assumes that treatment $B_1$ is always deselected when possible, but that the sample sizes of $B_2$ and $B_3$ are as

| Case | Proportions | | | | | $\eta$ | $N$ |
|---|---|---|---|---|---|---|---|
| | $w_{A_1}$ | $w_{A_2}$ | $w_{B_1}$ | $w_{B_2}$ | $w_{B_3}$ | | |
| 0 – $A_1 \asymp A_2$, $B_1 \asymp B_2 \asymp B_3$ | $\frac{1}{4}$ | $\frac{1}{4}$ | $\frac{1}{6}$ | $\frac{1}{6}$ | $\frac{1}{6}$ | 4 | 247 |
| 1 – $A_2 \succ A_1$, $B_1 \asymp B_2 \asymp B_3$ | $\frac{1}{10}$ | $\frac{4}{10}$ | $\frac{1}{6}$ | $\frac{1}{6}$ | $\frac{1}{6}$ | 5.13 | 316 |
| 2 – $A_2 \succ A_1$, $B_3 \succ B_1$, $B_3 \succ B_2 \succ B_1$ | $\frac{1}{10}$ | $\frac{4}{10}$ | $\frac{3}{30}$ | $\frac{5}{30}$ | $\frac{7}{30}$ | 5.38 | 332 |
| 3 – $B_2 \succ B_1$, $B_3 \succ B_1$, $B_2 \asymp B_3$, $A_1 \asymp A_2$ | $\frac{1}{4}$ | $\frac{1}{4}$ | $\frac{1}{30}$ | $\frac{7}{30}$ | $\frac{7}{30}$ | 6.29 | 387 |
| 4 – $B_3 \succ B_1$, $B_3 \succ B_2 \succ B_1$, $A_1 \asymp A_2$ | $\frac{1}{4}$ | $\frac{1}{4}$ | $\frac{1}{30}$ | $\frac{5}{30}$ | $\frac{9}{30}$ | 6.37 | 392 |
| 5 – $B_3 \succ B_1$, $B_3 \succ B_2 \succ B_1$, $A_2 \succ A_1$ | $\frac{1}{10}$ | $\frac{4}{10}$ | $\frac{1}{30}$ | $\frac{5}{30}$ | $\frac{9}{30}$ | 6.45 | 397 |
| 6 – $B_3 \succ B_2 \succ B_1$ and $A_2 \succ A_1$ simultaneously (not possible in theory and practice) | $\frac{1}{10}$ | $\frac{4}{10}$ | $\frac{1}{30}$ | $\frac{5}{30}$ | $\frac{9}{30}$ | 7.50 | 461 |
| 7 – NeSSy | $\frac{27}{149}$ | $\frac{42}{149}$ | $\frac{25}{149}$ | $\frac{23}{149}$ | $\frac{32}{149}$ | 4.17 | 258 |

Table 5.2: Proportions $w_{A_1}$, $w_{A_2}$, $w_{B_1}$, $w_{B_2}$ and $w_{B_3}$, $\eta$ and the total sample size for different allocations of treatments' sample sizes in the NeSSy design $\text{POR}_{2,3}$.

unbalanced as possible. The sample sizes of case 1 and case 3 illustrate the fact that imbalances in the strategy with more treatments weight more heavily. Case 5 follows case 4, except that the treatments in strategy $\mathcal{A}$ are now as unequally represented as possible. The difference between case 4 and 5 in the calculated total sample size is small compared to the differences from case 0 to 5. Case 6 describes a scenario that is not possible in theory and in practice in a $\text{POR}_{k,l}$ design. The treatments in both strategies take their maximal unbalanced case in each strategy. However, this case shows what could happen in the CUtLASS design if not the strategy is used as factor in the one-way classification, but the treatments together with a strategy comparison contrast. The treatments with only one patient would increase the sample sizes enormously.

Case 7 in Table 5.2 shows the observed allocation in the NeSSy study with total sample size close to the balanced scenario. This demonstrates that case 1 to case 5 include strong assumptions on the distribution of the treatments' sample sizes. We can see that the assumptions on the physician's selection behaviour have a large impact on the computed sample size. Therefore, those assumptions should be made with care and be well justified. It may be advisable to do a recalculation of the sample size after a certain number of patients are randomised. This way, one could make use of the observed allocation of the patients in order to gain a more correct sample size calculation. Figure 5.1 illustrates the linearity between the different $\eta$s for case 0 to 7 of Table 5.2 and $N$ in the $\text{POR}_{2,3}$ design with the assumptions from Table 5.2 for $\Delta$, $\sigma_\varepsilon$, $\alpha$ and $\beta$.

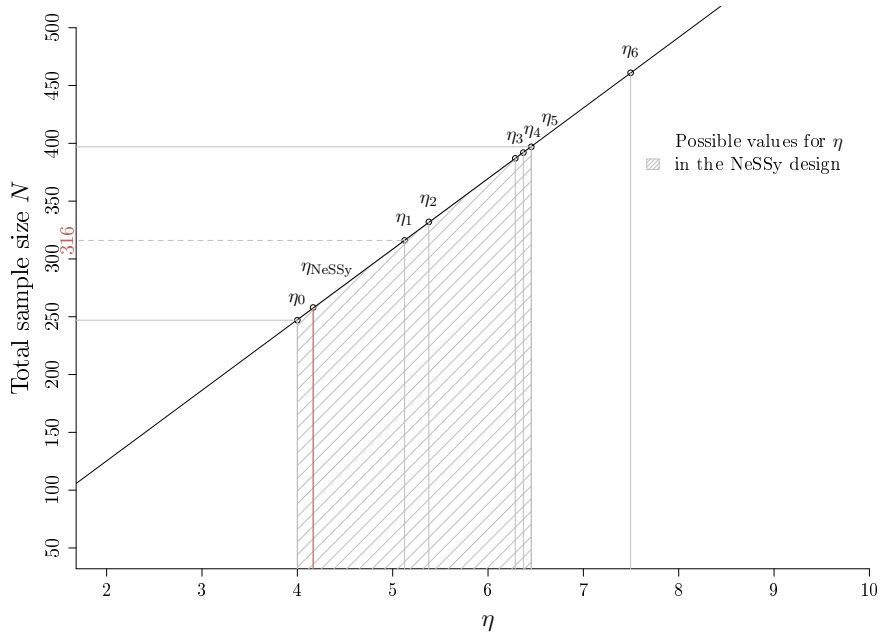



Figure 5.1: Dependence between total sample size $N$ and allocation of sample sizes in all treatments using the parameter $\eta$ in the NeSSy design.

If the number of treatments in strategy $\mathcal{A}$ is smaller than the number of treatments in strategy $\mathcal{B}$, we can assume that case 5 of Table 5.2 is a good lower bound for the maximum of $\eta$ for the $\text{POR}_{2,3}$ design. For $k = l$ it is possible to find an allocation leading to a larger $\eta$ than that of case 5. For example in a $\text{POR}_{3,3}$ design, the weighting factor $c_j^2$ in the calculation of $\eta$ is the same in both strategies. Therefore, we can take the minimum proportion in one strategy, e.g. strategy $\mathcal{B}$, and search for the next smallest possible proportion in both strategies. Our investigations show that this would be strategy $\mathcal{A}$. If we continue with minimisation for $w_j$ in both strategies, we obtain a larger $\eta$ than that the approach of case 5 leads to.

For case 1, 3 to 5, we determine general formulas for the proportions.

**Property 5.5.2.** *Given a* $\text{POR}_{k,l}$ *design, the following statements are true.*

1. *If only treatment* $A_1$ *is deselected when possible and all other treatments' sample sizes are balanced, i.e.* $A_i \asymp A_1$ *for all* $i = 2, \ldots, k$ *and* $B_j \asymp B_{j'}$ *for* $j, j' = 1, \ldots, l$*, then the following proportions are obtained*

$$
\begin{aligned}
w_{A_1} &= \frac{l-1}{2k(kl-1)} \\
w_{A_i} &= \frac{k^2 l - k - l + 1}{2k(kl-1)(k-1)} && \text{for} \quad i = 2, \ldots, k \\
w_{B_j} &= \frac{1}{2l} && \text{for} \quad j = 1, \ldots, l.
\end{aligned}
$$

2. *Let the treatments of strategy* $\mathcal{A}$ *be selected and deselected with* $A_{i'} \succ A_i$ *for* $i' > i$ *and the treatments' sample sizes of strategy* $\mathcal{B}$ *be balanced* ($B_j \asymp B_{j'}$ *for* $j, j' = 1, \ldots, l$).

*Then the following proportions are obtained*

$$w_{A_i} = \frac{(2i-1)l-1}{2k(kl-1)} \qquad \text{for} \quad i = 1, \ldots, k$$
$$w_{B_j} = \frac{1}{2l} \qquad \text{for} \quad j = 1, \ldots, l.$$

3. *If only treatment $B_1$ is deselected when possible and all other treatments' sample sizes are balanced, i.e. $B_j \asymp B_1$ for all $j = 2, \ldots, l$ and $A_i \asymp A_{i'}$ for $i, i' = 1, \ldots, k$, then we obtain the proportions*

$$w_{A_i} = \frac{1}{2k} \qquad \text{for} \quad i = 1, \ldots, k$$
$$w_{B_1} = \frac{k-1}{2l(kl-1)}$$
$$w_{B_j} = \frac{kl^2-k-l+1}{2l(kl-1)(l-1)} \qquad \text{for} \quad j = 2, \ldots, l.$$

4. *Let the treatments of strategy $\mathcal{B}$ be selected and deselected with $B_{j'} \succ B_j$ for $j' > j$ and the treatments' sample sizes of strategy $\mathcal{A}$ be balanced ($A_i \asymp A_{i'}$ for $i, i' = 1, \ldots, k$). Then the proportions*

$$w_{A_i} = \frac{1}{2k} \qquad \text{for} \quad i = 1, \ldots, k$$
$$w_{B_j} = \frac{(2j-1)k-1}{2l(kl-1)} \qquad \text{for} \quad j = 1, \ldots, l$$

*are obtained.*

5. *Let the treatments of strategy $\mathcal{B}$ be selected and deselected with $B_{j'} \succ B_j$ for $j' > j$ and afterwards, let the treatments of strategy $\mathcal{A}$ be selected and deselected with $A_{i'} \succ A_i$ for $i' > i$. Then the following proportions are obtained*

$$w_{A_i} = \frac{kl-k+2(i-1)}{2k(kl-1)} \qquad \text{for} \quad i = 1, \ldots, k$$
$$w_{B_j} = \frac{(2j-1)k-1}{2l(kl-1)} \qquad \text{for} \quad j = 1, \ldots, l.$$

*Proof.*

1. If treatment $A_1$ is deselected when possible, the proportion $w_{A_1}$ takes the minimum allocation probability from Property 3.2.2. Since $\sum_{i=1}^{k} w_{A_i} = p_\psi$, we have that $\sum_{j=2}^{l} w_{A_i} = p_\psi - w_{A_1}$. Furthermore, we have that $w_{A_i} = w_{A_{i'}}$ for $i, i' \geq 2$, and consequently

$$\begin{aligned} w_{A_i} &= \frac{p_\Psi - w_{A_1}}{k-1} \\ &= \left(\frac{1}{2} - \frac{l-1}{2k(kl-1)}\right)\frac{1}{k-1} \\ &= \frac{k^2l-k-l+1}{2k(kl-1)(k-1)} \end{aligned}$$

for $i = 2, \ldots, k$. For the treatments of strategy $\mathcal{B}$ we split $1 - p_\Psi = 1/2$ in $l$ equal proportions

$$w_{B_j} = \frac{1}{2l} \quad \text{for} \quad j = 1, \ldots, l.$$

2. We receive as before

$$w_{A_1} = \frac{l-1}{2k(kl-1)}$$

for the proportion of $A_1$. For $w_{A_2}$, the proportion takes also the minimum allocation probability, but, in addition, in all two-pair combinations with a mixed $\mathcal{A}$-pair $[A_1, A_2]$, we prefer the random pair with treatment $A_2$. From Equation (2.7), we know that the probability for mixed $\mathcal{A}$-pairs is $q_\mathcal{A} = 2l/k(kl-1)$. Taking into account that it is possible to randomise in strategy $\mathcal{B}$ with a probability of $p_\Psi = 1/2$, we obtain

$$\begin{aligned} w_{A_2} &= \frac{l-1}{2k(kl-1)} + \frac{1}{2}\frac{2l}{k(kl-1)} \\ &= \frac{3l-1}{2k(kl-1)}. \end{aligned}$$

In the same way we have for the proportion of treatment $A_i$ ($i \leq k$ fixed but arbitrary) $i-1$ distinct mixed $\mathcal{A}$-pairs $[A_{i'}, A_i]$ ($i' = 1, \ldots, i-1$) with the same probability $p_\Psi p_\mathcal{A}$ as before. Hence, we obtain

$$\begin{aligned} w_{A_i} &= \frac{l-1}{2k(kl-1)} + \frac{1}{2}\frac{2l}{k(kl-1)}(i-1) \\ &= \frac{(2i-1)l-1}{2k(kl-1)}. \end{aligned}$$

The considerations for the proportions of strategy $\mathcal{B}$ are the same as before under point 1.

3.-4. Follows form 1. and 2. by symmetry.

5. The proportions of patients per treatment in strategy $\mathcal{B}$ are the same as in 4. If we choose all random pairs in the two-pair combination due to preferences in strategy $\mathcal{B}$, we only have the $\mathcal{A}$-informative combinations to take the preferences of strategy $\mathcal{A}$ into account. In each $\mathcal{A}$-informative combination, treatment $A_1$ can be deselected. Therefore, we have to determine the number of two-pair combinations in which treatment $A_1$ is possible after decisions in strategy $\mathcal{B}$. These two-pair combinations are the $\mathcal{B}$-informative combinations with identical $\mathcal{A}$-pair $[A_1, A_1]$ and the mixed combinations. In the $\mathcal{B}$-informative combinations, the physician's choice in strategy $\mathcal{B}$ does not matter if the second randomisation step randomises the patient to strategy $\mathcal{A}$. In the mixed combinations, the physician's decision in strategy $\mathcal{B}$ leads to equally often presented treatments in strategy $\mathcal{A}$ in the chosen random pairs. To determine the total number of mixed combinations, we subtract the number of clear patient-oriented decisions from the number of two-pair combinations

$$|\mathcal{TPC}_{k,l}| - |\mathrm{POD}_{k,l}| = \frac{kl(kl-1)}{2} - \frac{kl(l+k-2)}{2}$$

$$= \frac{kl(kl-l-k+1)}{2}$$
$$= \frac{kl(k-1)(l-1)}{2}.$$

Summing up the $l(l-1)/2$ $\mathcal{B}$-informative combinations with identical $\mathcal{A}$-pair $[A_1, A_1]$ and the $l(k-1)(l-1)/2$ mixed combinations with treatment $A_1$ in the remaining random pair after physician's decisions in strategy $\mathcal{B}$, we have

$$\frac{l(l-1)}{2} + \frac{l(k-1)(l-1)}{2} = \frac{l(l-1)(k-1+1)}{2}$$
$$= \frac{kl(l-1)}{2}$$

two-pair combinations, where treatment $A_1$ is present in the chosen random pair. Hence the proportion of these two-pair combinations is

$$\frac{kl(l-1)}{2}\frac{2}{kl(kl-1)} = \frac{l-1}{kl-1}.$$

Since strategy $\mathcal{A}$ is randomised with probability $p_\Psi = 1/2$ the proportion of patients receiving treatment $A_1$ after the selection of random pairs due to the preferences in strategy $\mathcal{B}$ is given by

$$w_{A_1} = \frac{1}{2}\frac{l-1}{kl-1}$$
$$= \frac{l-1}{2(kl-1)}.$$

Obviously, $w_{A_2}$ is equal to $w_{A_1}$ plus the proportion of cases where we have the mixed $\mathcal{A}$-pair $[A_1, A_2]$ in the $\mathcal{A}$-informative combinations multiplied with $p_\Psi = 1/2$. Each $\mathcal{A}$-informative combination appears $l$ times (once with each of the $l$ distinct identical $\mathcal{B}$-pairs). Hence we have

$$w_{A_2} = w_{A_1} + \frac{l}{kl(kl-1)}$$
$$= \frac{l-1}{2(kl-1)} + \frac{l}{kl(kl-1)}$$
$$= \frac{kl-k+2}{2k(kl-1)}.$$

In the same way, we have for the proportion of treatment $A_i$ ($i \leq k$ fixed but arbitrary) $i-1$ distinct mixed $\mathcal{A}$-pairs $[A_{i'}, A_i]$ (for $i' = 1, \ldots, i-1$) with the same probability $l/kl(kl-1)$ as before. Hence, we obtain

$$w_{A_i} = \frac{l-1}{2(kl-1)} + \frac{l}{kl(kl-1)}(i-1)$$
$$= \frac{kl-k+2(i-1)}{2k(kl-1)}.$$

□

**Example.** Table 5.3 shows $\eta$ for the five cases of allocation of treatments' sample sizes from Property 5.5.2 in the patient-oriented randomisation designs

| $k$ | Allocation of treatments' sample sizes | $l$ | 2 | 3 | 4 |
|---|---|---|---|---|---|
| 2 | 1. $A_2 \succ A_1$, $B_j \asymp \mathcal{B}_{j-1}$ for $j = 2, \ldots, l$ | | 5.60 | 5.13 | 4.97 |
| | 2. $A_2 \succ A_1$, $B_j \asymp \mathcal{B}_{j-1}$ for $j = 2, \ldots, l$ | | 5.60 | 5.13 | 4.97 |
| | 3. $B_2 \succ B_1$, $B_j \succ B_1$, $B_j \asymp \mathcal{B}_{j-1}$ for $j = 3, \ldots, l$, $A_2 \asymp A_1$ | | 5.60 | 6.29 | 6.67 |
| | 4. $B_{j'} \succ B_j$ for $j = 1, \ldots, l-1$ and $j' = 2, \ldots, l$ with $j' > j$, $A_2 \asymp A_1$ | | 5.60 | 6.37 | 6.86 |
| | 5. $B_{j'} \succ B_j$ for $j = 1, \ldots, l-1$ and $j' = 2, \ldots, l$ with $j' > j$, $A_2 \succ A_1$ | | 5.85 | 6.45 | 6.90 |
| 3 | 1. $A_3 \succ A_1$, $A_2 \succ A_1$, $A_3 \asymp A_2$, $B_j \asymp \mathcal{B}_{j-1}$ for $j = 2, \ldots, l$ | | - | 5.64 | 5.42 |
| | 2. $A_2 \succ A_1$, $A_3 \succ A_1$, $A_3 \succ A_2$, $B_j \asymp \mathcal{B}_{j-1}$ for $j = 2, \ldots, l$ | | - | 5.71 | 5.50 |
| | 3. $B_2 \succ B_1$, $B_j \succ B_1$, $B_j \asymp \mathcal{B}_{j-1}$ for $j = 3, \ldots, l$, $A_3 \asymp A_2 \asymp A_1$ | | - | 5.64 | 5.93 |
| | 4. $B_{j'} \succ B_j$ for $j = 1, \ldots, l-1$ and $j' = 2, \ldots, l$ with $j' > j$, $A_3 \asymp A_2 \asymp A_1$ | | - | 5.71 | 6.11 |
| | 5. $B_{j'} \succ B_j$ for $j = 1, \ldots, l-1$ and $j' = 2, \ldots, l$ with $j' > j$, $A_2 \succ A_1$, $A_3 \succ A_1$, $A_3 \succ A_2$ | | - | 5.80 | 6.15 |

Table 5.3: Parameter $\eta$ for different allocations of treatments' sample sizes in different $\text{POR}_{k,l}$ designs.

$\text{POR}_{2,2}$, $\text{POR}_{2,3}$, $\text{POR}_{2,4}$, $\text{POR}_{3,3}$ and $\text{POR}_{3,4}$. Thereby, only the $\eta$s of one design can be compared against each other, since the assumptions for $\Delta$, $\sigma_\varepsilon$ for the sample size calculation as well as the number of terms in $\eta$ change between different designs.

For the $\text{POR}_{2,l}$ designs, $l = 2, \ldots, 4$, we see that the first and the second allocation of the treatments' sample sizes are the same, likewise the third and the fourth allocation of $\text{POR}_{2,2}$. We also see that the first and the third and the second and the fourth allocation of designs with the same number of treatments in both strategies lead to the same $\eta$ due to symmetry. However, the fifth allocation has the largest $\eta$ in all designs.

**Remark.** We also can use Model (5.1) and the strategy comparison contrast (5.9) for the $\text{CUtLASS}_{k,l}$ and $\text{Block}_{k,l}$ designs. For the power calculation, only the assumptions on the effect between both strategies $\Delta$ and $\eta$ change. For the $\text{Block}_{k,l}$ design, the proportions coincide with the balanced case of the $\text{POR}_{k,l}$ design (see Equation (5.17)) and lead to $\eta = 4$. For the $\text{CUtLASS}_{k,l}$ design, it is not as simple to determine $\eta$ as in the $\text{Block}_{k,l}$ and the $\text{POR}_{k,l}$ designs. In the best case, the treatments' sample sizes are balanced in each strategy and we also obtain $\eta = 4$. In the worst case, each treatment except one is represented with one patient in each strategy. Then, the proportions depend inversely on the total sample size $N$ and lead to a large $\eta$. In order to prevent a large sample size or a decrease in the power, the $\text{CUtLASS}_{k,l}$ design should use Model (5.1) with strategy as factor. The assumption for the effect between both strategies $\Delta$ may be changed between the three design types, in the following section we will see why.

## 5.6 Strategy comparison in POR, CUtLASS and Block—an example

When allowing for a patient-oriented decision in the randomisation process (as is done in the CUtLASS and the POR design) the observed treatment effects also depend on the physicians' decision. In this section, we will investigate how the randomisation design, the physician's decisions (i.e. the frequency of 'optimal' decisions as defined below) and the heterogeneity of the study population (cf. the example of Section 1.3) affect the treatment effect under consideration. Furthermore, we investigate the difference in treatment effects when using strategy instead of treatments as factor in model (5.1).

**Example.** Let us consider a hypothetical clinical trial comparing two different strategies $\mathcal{A}$ and $\mathcal{B}$. Each strategy consists of two different treatments: $A_1$, $A_2 \in \mathcal{A}$ and $B_1$, $B_2 \in \mathcal{B}$. We also suppose that we have two different population types $P_1$ and $P_2$, not necessarily of similar size. The proportion of population type $P_1$ in the total population is specified by $\kappa$ with $\kappa \in [0,1]$ and the proportion of population type $P_2$ with $(1-\kappa)$. In practice, we do not know which patient belongs to which population and how large the groups are.

To simplify the example, we assume that patients of populations $P_1$ and $P_2$ respond differently to the treatments of strategy $\mathcal{A}$, but similar to the treatments of strategy $\mathcal{B}$. We also assume that the error variance $\sigma_\varepsilon^2$ is the same for all patients independent from treatment and population. The treatment means in strategy $\mathcal{A}$ of the different populations are denoted by $\mu_{A_1P_1}$, $\mu_{A_1P_2}$, $\mu_{A_2P_1}$ and $\mu_{A_2P_2}$ and the treatment means in strategy $\mathcal{B}$ by $\mu_{B_1P_1}$, $\mu_{B_1P_2}$, $\mu_{B_2P_1}$ and $\mu_{B_2P_2}$ where $\mu_{B_1P_1} = \mu_{B_1P_2} = \mu_{B_2P_1} = \mu_{B_2P_2} = \mu_{\mathcal{B}}$. We assume that patients in $P_1$ have a better response to $A_1$ than to $A_2$ and conversely patients in $P_2$ have a better response to $A_2$ than to $A_1$, i.e. $\mu_{A_1P_1} > \mu_{A_2P_1}$ and $\mu_{A_2P_2} > \mu_{A_1P_2}$.

Additionally, we define $\rho$ as the probability that a physician chooses the most suitable random pair from a two-pair combination for a given patient whenever possible. In the set-up considered here, this means selection of a random pair with the $\mathcal{A}$-treatment which has a higher treatment mean in the population the patient belongs to, whenever mixed $\mathcal{A}$-pairs are present. Of course, there can be no 'best' or 'worst' decision when the given two-pair combination has an identical $\mathcal{A}$-pair, because the treatment means for the $\mathcal{B}$-treatments are assumed to be equal for all patients. We assume that $\rho$ is equal for all physicians. Obviously, we have $\rho \in [0,1]$, where $\rho = 1$ means that the physicians decisions are always optimal and $\rho = 0$ describes the case where the random pair with the best treatment is never selected. Since the physicians do not know which sub-population a specific patient belongs to, we expect $\rho \in (0,1)$ in practice. However, this is not an assumption made here.

It is easy to see that for $\rho = 0.5$, the POR and the CUtLASS design lead to the same distribution of patients to the treatment groups and thereby to the same expected treatment effects.

### Block$_{2,2}$ design

The probability that a given patient in the study is in population $P_i$, $i = 1, 2$, and receives treatment $A_1$, $A_2$, $B_1$ or $B_2$ is $\kappa/4$ or $(1-\kappa)/4$ depending on population and treatment (see Table 5.4). The treatment mean of treatment $j$ consists of the proportions of patients with the $j$th treatment in the populations $P_1$ and $P_2$ as well as the treatment means of the $j$th treatment in these populations, i.e.

$$\mu_{A_1}^{\text{Block}} = \frac{\frac{1}{4}\kappa}{\frac{1}{4}}\mu_{A_1P_1} + \frac{\frac{1}{4}(1-\kappa)}{\frac{1}{4}}\mu_{A_1P_2} = \kappa\mu_{A_1P_1} + (1-\kappa)\mu_{A_1P_2}.$$

| Strategy | Treatment | Probability distribution in population type | | Cumulative frequencies in | |
|---|---|---|---|---|---|
| | | $P_1$ | $P_2$ | Treatment | Strategies |
| $\mathcal{A}$ | $A_1$ | $\frac{1}{4}\kappa$ | $\frac{1}{4}(1-\kappa)$ | $\frac{1}{4}$ | $\frac{1}{2}$ |
| | $A_2$ | $\frac{1}{4}\kappa$ | $\frac{1}{4}(1-\kappa)$ | $\frac{1}{4}$ | |
| $\mathcal{B}$ | $B_1$ | $\frac{1}{4}\kappa$ | $\frac{1}{4}(1-\kappa)$ | $\frac{1}{4}$ | $\frac{1}{2}$ |
| | $B_2$ | $\frac{1}{4}\kappa$ | $\frac{1}{4}(1-\kappa)$ | $\frac{1}{4}$ | |
| Cumulative frequencies | | $\kappa$ | $1-\kappa$ | 1 | 1 |

Table 5.4: Probability distribution for a patient to belong to population $P_i$, $i = 1, 2$, and to receive one of the four treatments $A_1$, $A_2$, $B_1$ and $B_2$ in the $\text{Block}_{2,2}$ design.

Similiarly, we obtain

$$\begin{aligned}
\mu_{A_2}^{\text{Block}} &= \kappa\mu_{A_2P_1} + (1-\kappa)\mu_{A_2P_2},\\
\mu_{B_1}^{\text{Block}} &= \kappa\mu_{B_1P_1} + (1-\kappa)\mu_{B_1P_2} = \mu_{\mathcal{B}},\\
\mu_{B_2}^{\text{Block}} &= \kappa\mu_{B_2P_1} + (1-\kappa)\mu_{B_2P_2} = \mu_{\mathcal{B}},\\
\mu_{\mathcal{A}}^{\text{Block}} &= \frac{1}{2}\kappa\mu_{A_1P_1} + \frac{1}{2}(1-\kappa)\mu_{A_1P_2} + \frac{1}{2}\kappa\mu_{A_2P_1} + \frac{1}{2}(1-\kappa)\mu_{A_2P_2},\\
\mu_{\mathcal{B}}^{\text{Block}} &= \frac{1}{2}\kappa\mu_{\mathcal{B}} + \frac{1}{2}(1-\kappa)\mu_{\mathcal{B}} + \frac{1}{2}\kappa\mu_{\mathcal{B}} + \frac{1}{2}(1-\kappa)\mu_{\mathcal{B}} = \mu_{\mathcal{B}}.
\end{aligned}$$

The components of the strategy comparison contrast are then given by

$$\frac{1}{2}\mu_{A_1}^{\text{Block}} + \frac{1}{2}\mu_{A_2}^{\text{Block}} = \frac{1}{2}\left(\kappa\mu_{A_1P_1} + (1-\kappa)\mu_{A_1P_2}\right) + \frac{1}{2}\left(\kappa\mu_{A_2P_1} + (1-\kappa)\mu_{A_2P_2}\right) = \mu_{\mathcal{A}}^{\text{Block}}$$

and

$$\frac{1}{2}\mu_{B_1}^{\text{Block}} + \frac{1}{2}\mu_{B_2}^{\text{Block}} = \mu_{\mathcal{B}}.$$

In the case of balanced sample size in all treatments in each strategy such as in the $\text{Block}_{2,2}$ design, the difference in strategy means coincides with the strategy comparison contrast, i.e.

$$\psi_0^{\text{Block}} = \frac{1}{2}\mu_{A_1}^{\text{Block}} + \frac{1}{2}\mu_{A_2}^{\text{Block}} - \frac{1}{2}\mu_{B_1}^{\text{Block}} - \frac{1}{2}\mu_{B_2}^{\text{Block}} = \mu_{\mathcal{A}}^{\text{Block}} - \mu_{B}^{\text{Block}}.$$

### $\text{POR}_{2,2}$ design

As for the $\text{Block}_{2,2}$ design we are interested in the probabilities that a patient entering the study will be in a specific population ($P_1$ or $P_2$) and receives a specific treatment in the $\text{POR}_{2,2}$ design. Unlike in the $\text{Block}_{2,2}$ design the physicians decision has now influence on there probabilities.

As described above, we assume a different response behaviour for the subjects of $P_1$ and $P_2$ to the treatments of strategy $\mathcal{A}$ ($\mu_{A_1P_1} > \mu_{A_2P_1}$ and $\mu_{A_2P_2} > \mu_{A_1P_2}$). Further-

more, we assume that the physician chooses the random pair of a two-pair combination which includes the $\mathcal{A}$-treatment with better response for each patient (depending on the population $P_i$) with probability $\rho$ whenever possible (see above).

The probability that a patient entering the study will be in a specific population ($P_1$ or $P_2$) and receive a specific treatment can be decomposed in the conditional probability of receiving the treatment given the population and the randomised strategy and the joint probability of being in the specific strategy. The latter probability is $\kappa/2$ for population $P_1$ and $(1-\kappa)/2$ for population $P_2$. To determine the mentioned conditional probability we have a look at Table 5.5. In this table, we find the conditional probability of receiving a specific treatment given the two-pair combination, the population and randomisation to the corresponding strategy. In the last row ('relative frequencies'), we find the desired conditional probability mentioned above. The numbers in Table 5.5 are the result of the following considerations. In two-pair combination 1 and 6, the physician can not decide between the treatments of strategy $\mathcal{A}$. Since we assume that treatments $B_1$ and $B_2$ are equally preferred, in half of the cases the patient will receive treatment $B_1$ and otherwise $B_2$ independent of the population of the patient. For two-pair combinations 2 to 5, the physician should decide for a patient of population $P_1$ for treatment $A_1$ and otherwise for a patient of population $P_2$ for treatment $A_2$. This is done with probability $\rho$. Summing up over all two-pair combinations we obtain the cumulative frequencies. Dividing them by the number of two-pair combinations leads to the relative frequencies. Combining there with the probabilities $\kappa/2$ respectively $(1-\kappa)/2$ leads to the probability distribution in Table 5.6.

| TPC | $\mathcal{TPC}_{2,2}$ | Patient-oriented decision in strategy $\mathcal{A}$ for a patient in $P_1$ | | $\mathcal{A}$ for a patient in $P_2$ | | $\mathcal{B}$ for a patient in $P_1$ | | $\mathcal{B}$ for a patient in $P_2$ | |
|---|---|---|---|---|---|---|---|---|---|
| | | $A_1$ | $A_2$ | $A_1$ | $A_2$ | $B_1$ | $B_2$ | $B_1$ | $B_2$ |
| 1 | $[(A_1,B_1),(A_1,B_2)]$ | 1 | 0 | 1 | 0 | $\frac{1}{2}$ | $\frac{1}{2}$ | $\frac{1}{2}$ | $\frac{1}{2}$ |
| 2 | $[(A_1,B_1),(A_2,B_1)]$ | $\rho$ | $1-\rho$ | $1-\rho$ | $\rho$ | 1 | 0 | 1 | 0 |
| 3 | $[(A_1,B_1),(A_2,B_2)]$ | $\rho$ | $1-\rho$ | $1-\rho$ | $\rho$ | $\rho$ | $1-\rho$ | $1-\rho$ | $\rho$ |
| 4 | $[(A_1,B_2),(A_2,B_1)]$ | $\rho$ | $1-\rho$ | $1-\rho$ | $\rho$ | $1-\rho$ | $\rho$ | $\rho$ | $1-\rho$ |
| 5 | $[(A_1,B_2),(A_2,B_2)]$ | $\rho$ | $1-\rho$ | $1-\rho$ | $\rho$ | 0 | 1 | 0 | 1 |
| 6 | $[(A_2,B_1),(A_2,B_2)]$ | – | 1 | 0 | 1 | $\frac{1}{2}$ | $\frac{1}{2}$ | $\frac{1}{2}$ | $\frac{1}{2}$ |
| Cumulative frequencies | | $1+4\rho$ | $5-4\rho$ | $5-4\rho$ | $1+4\rho$ | 3 | 3 | 3 | 3 |
| Relative frequencies | | $\frac{1+4\rho}{6}$ | $\frac{5-4\rho}{6}$ | $\frac{5-4\rho}{6}$ | $\frac{1+4\rho}{6}$ | $\frac{1}{2}$ | $\frac{1}{2}$ | $\frac{1}{2}$ | $\frac{1}{2}$ |

Table 5.5: Probability to receive a specific treatment, given the two-pair combination, the population and randomisation to the corresponding strategy in the $\mathrm{POR}_{2,2}$ design.

This shows the probability distribution for a patient to belong to population $P_i$, $i=1,2$, and to receive one of the four treatments $A_1$, $A_2$, $B_1$ and $B_2$. We see that this distribution depends on the quality of physicians' decision measured by $\rho$ (see Table 5.6).

| Strategy | Treatment | Probability distribution in population type | | Cumulative frequencies in | |
|---|---|---|---|---|---|
| | | $P_1$ | $P_2$ | Treatment | Strategies |
| $\mathcal{A}$ | $A_1$ | $\frac{1+4\rho}{12}\kappa$ | $\frac{5-4\rho}{12}(1-\kappa)$ | $\frac{5-4\rho-4\kappa+8\kappa\rho}{12}$ | $\frac{1}{2}$ |
| | $A_2$ | $\frac{5-4\rho}{12}\kappa$ | $\frac{1+4\rho}{12}(1-\kappa)$ | $\frac{1+4\rho+4\kappa-8\kappa\rho}{4}$ | |
| $\mathcal{B}$ | $B_1$ | $\frac{1}{4}\kappa$ | $\frac{1}{4}(1-\kappa)$ | $\frac{1}{4}$ | $\frac{1}{2}$ |
| | $B_2$ | $\frac{1}{4}\kappa$ | $\frac{1}{4}(1-\kappa)$ | $\frac{1}{4}$ | |
| Cumulative frequencies | | $\kappa$ | $1-\kappa$ | 1 | 1 |

Table 5.6: Probability distribution for a patient to belong to population $P_i$, $i = 1, 2$, and to receive one of the four treatments $A_1$, $A_2$, $B_1$ and $B_2$ in the $\text{POR}_{2,2}$ design.

Similar to the $\text{Block}_{2,2}$ design, the treatment mean of treatment $j$ consists of the proportions of patients with the $j$th treatment in the populations $P_1$ and $P_2$ as well as the treatment means of the $j$th treatment in these populations. Since the probabilities of treatments of strategy $\mathcal{B}$ do not change compared to the $\text{Block}_{2,2}$ design, we only consider the treatment means of strategy $\mathcal{A}$,

$$\mu_{A_1}^{\text{POR}} = \frac{(1+4\rho)\kappa}{5-4\rho-4\kappa+8\kappa\rho}\mu_{A_1P_1} + \frac{(5-4\rho)(1-\kappa)}{5-4\rho-4\kappa+8\kappa\rho}\mu_{A_1P_2},$$
$$\mu_{A_2}^{\text{POR}} = \frac{(5-4\rho)\kappa}{1+4\rho+4\kappa-8\kappa\rho}\mu_{A_2P_1} + \frac{(1+4\rho)(1-\kappa)}{1+4\rho+4\kappa-8\kappa\rho}\mu_{A_2P_2}$$

and

$$\mu_{\mathcal{A}}^{\text{POR}} = \frac{(1+4\rho)\kappa}{6}\mu_{A_1P_1} + \frac{(5-4\rho)(1-\kappa)}{6}\mu_{A_1P_2} + \frac{(5-4\rho)\kappa}{6}\mu_{A_2P_1} + \frac{(1+4\rho)(1-\kappa)}{6}\mu_{A_2P_2}.$$

The $\mathcal{A}$ component of the strategy comparison contrast results in

$$\frac{1}{2}\mu_{A_1}^{\text{POR}} + \frac{1}{2}\mu_{A_2}^{\text{POR}} = \frac{(1+4\rho)\kappa}{10-8\rho-8\kappa+16\kappa\rho}\mu_{A_1P_1} + \frac{(5-4\rho)(1-\kappa)}{10-8\rho-8\kappa+16\kappa\rho}\mu_{A_1P_2} + \frac{(5-4\rho)\kappa}{2+8\rho+8\kappa-16\kappa\rho}\mu_{A_2P_1} + \frac{(1+4\rho)(1-\kappa)}{2+8\rho+8\kappa-16\kappa\rho}\mu_{A_2P_2}.$$

Hence we see that in the $\text{POR}_{2,2}$ design, the difference in strategy means does generally not coincide with the strategy comparison contrast. An exception is the case of $\rho = 1/2$, where all treatment means are the same for the $\text{POR}_{2,2}$ and the $\text{Block}_{2,2}$ design. In particular, the difference of the strategy means and the strategy comparison contrast are the same.

### $\text{CUtLASS}_{2,2}$ design

Similar to the $\text{POR}_{2,2}$ design, the assumption on the different response of patients from different populations ($\mu_{A_1P_1} > \mu_{A_2P_1}$ and $\mu_{A_2P_2} > \mu_{A_1P_2}$) have to be taken into account to determine the probability distribution for a patient to belong to population $P_i$, $i = 1, 2$, and

to receive one of the four treatments $A_1$, $A_2$, $B_1$ and $B_2$ in the CUtLASS$_{2,2}$ design. The corresponding values can be found in Table 5.7. The physician chooses with $\rho$ treatment $A_1$ for patients from population $P_1$ as well as treatment $A_2$ for patients of population $P_2$. The factor 1/2 in the probabilities of strategy $\mathcal{A}$ are due to the design, since the probability of the patient to be randomised to strategy $\mathcal{A}$ is $p_\Psi = 1/2$.

| Strategy | Treatment | Probability distribution in population type | | Cumulative frequencies in | |
|---|---|---|---|---|---|
| | | $P_1$ | $P_2$ | Treatment | Strategies |
| $\mathcal{A}$ | $A_1$ | $\frac{1}{2}\rho\kappa$ | $\frac{1}{2}(1-\rho)(1-\kappa)$ | $\frac{1-\kappa-\rho+2\kappa\rho}{2}$ | $\frac{1}{2}$ |
| | $A_2$ | $\frac{1}{2}(1-\rho)\kappa$ | $\frac{1}{2}\rho(1-\kappa)$ | $\frac{\kappa+\rho-2\kappa\rho}{2}$ | |
| $\mathcal{B}$ | $B_1$ | $\frac{1}{4}\kappa$ | $\frac{1}{4}(1-\kappa)$ | $\frac{1}{4}$ | $\frac{1}{2}$ |
| | $B_2$ | $\frac{1}{4}\kappa$ | $\frac{1}{4}(1-\kappa)$ | $\frac{1}{4}$ | |
| Cumulative frequencies | | $\kappa$ | $1-\kappa$ | 1 | 1 |

Table 5.7: Probability distribution for a patient to belong to population $P_i$, $i = 1, 2$, and to receive one of the four treatments $A_1$, $A_2$, $B_1$ and $B_2$ in the CUtLASS$_{2,2}$ design.

Similar to the Block$_{2,2}$ and the POR$_{2,2}$ design, the treatment mean of treatment $j$ consists of the proportions of patients with the $j$th treatment in the populations $P_1$ and $P_2$ as well as the treatment means of the $j$th treatment in these populations. Since the probabilities of treatments of strategy $\mathcal{B}$ do not change compared to the other designs, we only consider the treatment means of strategy $\mathcal{A}$,

$$\begin{aligned}\mu_{A_1}^{\text{CUtLASS}} &= \frac{\rho\kappa}{1-\rho-\kappa+2\kappa\rho}\mu_{A_1P_1} + \frac{(1-\rho)(1-\kappa)}{1-\rho-\kappa+2\kappa\rho}\mu_{A_1P_2},\\ \mu_{A_2}^{\text{CUtLASS}} &= \frac{(1-\rho)\kappa}{\rho+\kappa-2\kappa\rho}\mu_{A_2P_1} + \frac{\rho(1-\kappa)}{\rho+\kappa-2\kappa\rho}\mu_{A_2P_2}\end{aligned}$$

and

$$\begin{aligned}\mu_{\mathcal{A}}^{\text{CUtLASS}} &= \rho\kappa\mu_{A_1P_1} + (1-\rho)(1-\kappa)\mu_{A_1P_2}\\ &\quad + (1-\rho)\kappa\mu_{A_2P_1} + \rho(1-\kappa)\mu_{A_2P_2}.\end{aligned}$$

The $\mathcal{A}$ component of the strategy comparison contrast results in

$$\begin{aligned}\frac{1}{2}\mu_{A_1}^{\text{CUtLASS}} + \frac{1}{2}\mu_{A_2}^{\text{CUtLASS}} &= \frac{\rho\kappa}{2-2\rho-2\kappa+4\kappa\rho}\mu_{A_1P_1} + \frac{(1-\rho)(1-\kappa)}{2-2\rho-2\kappa+4\kappa\rho}\mu_{A_1P_2}\\ &\quad + \frac{(1-\rho)\kappa}{2\rho+2\kappa-4\kappa\rho}\mu_{A_2P_1} + \frac{\rho(1-\kappa)}{2\rho+2\kappa-4\kappa\rho}\mu_{A_2P_2}.\end{aligned}$$

The means $\mu_{\mathcal{A}}^{\text{CUtLASS}}$ and $1/2\mu_{A_1}^{\text{CUtLASS}} + 1/2\mu_{A_2}^{\text{CUtLASS}}$ are not the same. Hence, we see that in a CUtLASS$_{2,2}$ design, the difference in strategy means does generally not coincide with the strategy comparison contrast. An exception is the case $\rho = 1/2$, where all

treatment means are the same for the $\text{CUtLASS}_{2,2}$ and the $\text{Block}_{2,2}$ design. In particular, the difference of the strategy means and the strategy comparison contrast are the same.

**Example**

As further condition, we assume that $\mu_{\mathcal{A}} = \mu_B$. In this case, we have an effect neither between the strategy means nor in the strategy comparison contrast in the $\text{Block}_{2,2}$ design. Obviously, for $\rho = 1/2$, this also applies for the $\text{POR}_{2,2}$ and $\text{CUtLASS}_{2,2}$ designs. Furthermore, we consider the means of strategy $\mathcal{A}$ relative to those of strategy $\mathcal{B}$, i.e. for $a$, $b$, $c$, $d \in [0,1]$, we define

$$\begin{aligned} \mu_{A_1P_1} &= \mu_{\mathcal{B}}(1+a), \quad \mu_{A_1P_2} = \mu_{\mathcal{B}}(1-b), \\ \mu_{A_2P_1} &= \mu_{\mathcal{B}}(1-c), \quad \mu_{A_2P_2} = \mu_{\mathcal{B}}(1+d). \end{aligned}$$

To fulfil the condition $\mu_{\mathcal{A}}^{\text{Block}} = \mu_B$ in the $\text{Block}_{2,2}$ design with

$$\mu_{\mathcal{A}}^{\text{Block}} = \frac{1}{2}\kappa\mu_{A_1P_1} + \frac{1}{2}(1-\kappa)\mu_{A_1P_2} + \frac{1}{2}\kappa\mu_{A_2P_1} + \frac{1}{2}(1-\kappa)\mu_{A_2P_2},$$

we need to have $a + b - c - d = 0$ and $d - b = 0$, hence $a = c$ and $d = b$. With these conditions, we obtain

$$\mu_{\mathcal{A}}^{\text{POR}} = \mu_B \left(1 + \frac{4\rho - 2}{3}\left(a\kappa + b(1-\kappa)\right)\right), \tag{5.18}$$

$$\frac{1}{2}\mu_{A_1}^{\text{POR}} + \frac{1}{2}\mu_{A_2}^{\text{POR}} = \mu_{\mathcal{B}} \left(1 + \frac{12\kappa(1-\kappa)(2\rho-1)}{16\kappa(1-\kappa)(2\rho-1)^2 + 16\rho(1-\rho) + 5}(a+b)\right) \tag{5.19}$$

for the means of the $\text{POR}_{2,2}$ design and

$$\mu_{\mathcal{A}}^{\text{CUtLASS}} = \mu_B \left(1 + (2\rho-1)\left(a\kappa + b(1-\kappa)\right)\right), \tag{5.20}$$

$$\frac{1}{2}\mu_{A_1}^{\text{CUtLASS}} + \frac{1}{2}\mu_{A_2}^{\text{CUtLASS}} = \mu_{\mathcal{B}} \left(1 + \frac{\kappa(1-\kappa)(2\rho-1)}{2\kappa(1-\kappa)(2\rho-1)^2 + 2\rho(1-\rho)}(a+b)\right) \tag{5.21}$$

for the $\text{CUtLASS}_{2,2}$ design means. All means of strategy $\mathcal{A}$ are multiples of $\mu_{\mathcal{B}}$. When determining the strategy differences, respectively the strategy comparison contrast, we subtract $\mu_{\mathcal{B}}$ from (5.18)–(5.21) and obtain a multiple of $\mu_{\mathcal{B}}$ itself. The corresponding factor (i.e. the second summand in the brackets) is called relative effect and is denoted by $\nabla$ for the relative effect of the strategy mean differences and $\nabla_{\text{SCC}}$ for the relative effect of the strategy comparison contrast. The relative effects of the strategy mean differences, respectively the strategy comparison contrast, depend on $\kappa$, $\rho$, $a$, $b$ and the type of design. We see that the size of the populations ($\kappa$) and the relative effect size in these populations ($a$ and $b$) are included together in the relative effects of the strategy comparison contrasts of both designs and cannot be separated. However, in the relative effect of the strategy comparison contrast, they are separated in both designs. Therefore, the behaviour of $\nabla$ and $\nabla_{\text{SCC}}$ are different in each design. For the parameters $a$, $b$, we consider two different models.

- Model 1: $a = b = 0.5$, i.e. treatments $A_1$ and $A_2$ differ in efficacy in the different populations, the effect of the more suitable $\mathcal{A}$-treatment is the same in both populations.

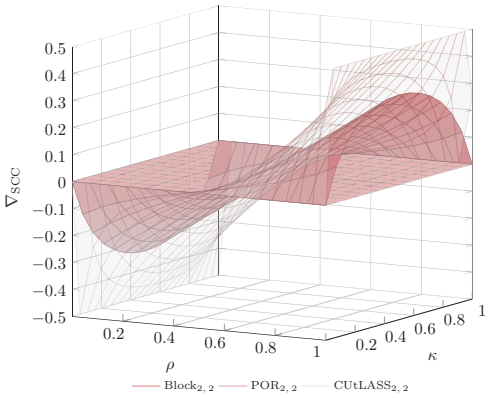
- Model 2: $a = 0.5$, $b = 0$, i.e. treatments $A_1$ and $A_2$ differ in efficacy in the different populations, but the effect is the same in population $P_2$.

In Panels a)–f) of Figure 5.2, the results of the relative effects $\nabla$ and $\nabla_{\text{scc}}$ depending on $\kappa$ and $\rho$ are presented. Panel a) of Figure 5.2 compare the strategy comparison contrast of the three randomisation designs in model 1. We see that the $\text{CUtLASS}_{2,2}$ design has a larger relative effect than the other designs for $\rho > 0$. If we change the size of $a$ and $b$, only the height of plans will change, not the position to each other, because the sum of $a$ and $b$ works in Equations (5.19) and (5.21) such as scaling factor.

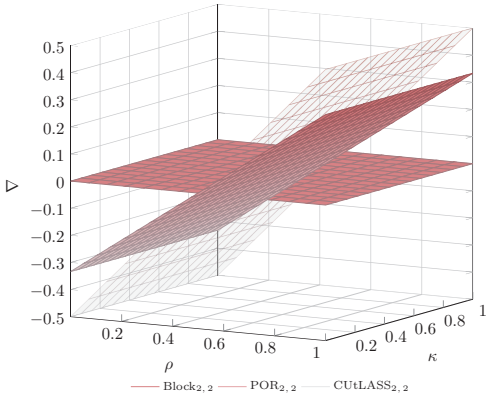
Panel b) of Figure 5.2 compares the differences in strategy means in the three designs in model 1. The position of three planes to each other is the same in model 2. Furthermore, the relative effect is larger in the $\text{CUtLASS}_{2,2}$ than in the $\text{POR}_{2,2}$ design for $\rho > 0.5$.

Panels c)–d) of Figure 5.2 show the strategy difference and the strategy comparison contrast of the $\text{POR}_{2,2}$ design for the two models. We see that the course of the relative effect of the difference in strategy means depends on the model and on the composition of the populations. The picture is almost the same in the Panels e)–f) for the $\text{CUtLASS}_{2,2}$ design.

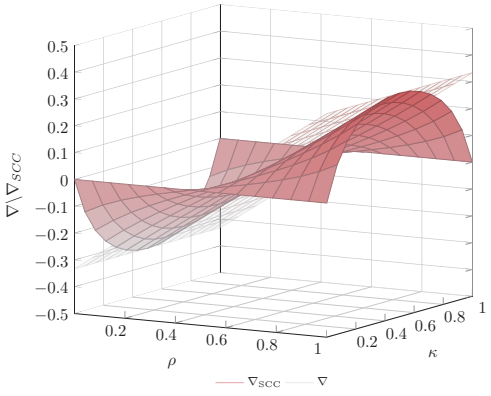
a) Strategy comparison contrast of $\text{Block}_{2,2}$, $\text{POR}_{2,2}$ and $\text{CUtLASS}_{2,2}$ in model 1 ($a = b = 0.5$)



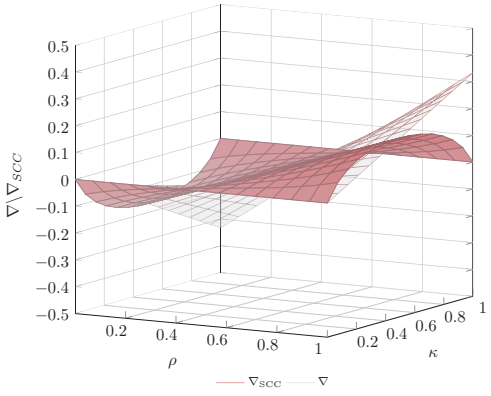

b) Strategy difference of $\text{Block}_{2,2}$, $\text{POR}_{2,2}$ and $\text{CUtLASS}_{2,2}$ in model 1 ($a = b = 0.5$)




c) Strategy comparison contrast and strategy difference of $\text{POR}_{2,2}$ in model 1 ($a = b = 0.5$)




d) Strategy comparison contrast and strategy difference of $\text{POR}_{2,2}$ in model 2 ($a = 0.5$, $b = 0$)



e) Strategy comparison contrast and strategy difference of $\text{CUtLASS}_{2,2}$ in model 1 ($a = b = 0.5$)

f) Strategy comparison contrast and strategy difference of $\text{CUtLASS}_{2,2}$ in model 2 ($a = 0.5$, $b = 0$)

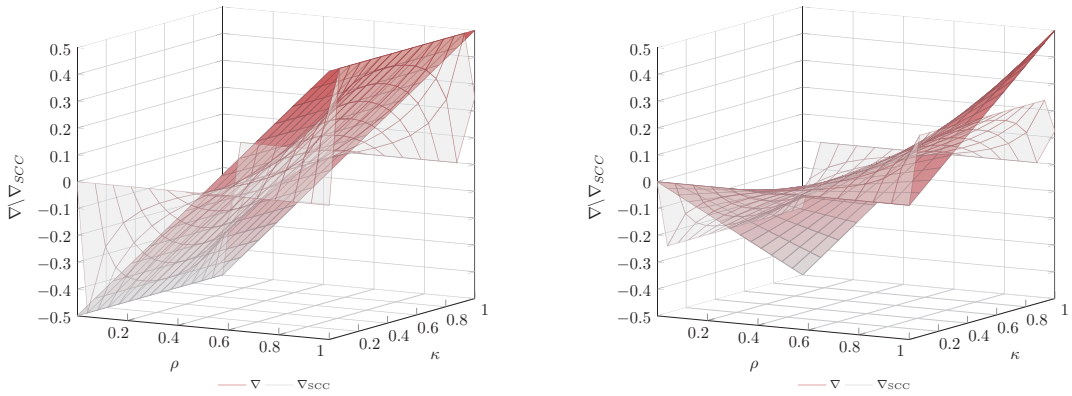



Figure 5.2: Relative effects $\nabla$ and $\nabla_{\text{SCC}}$ of the $\text{POR}_{2,2}$, $\text{CUtLASS}_{2,2}$ and $\text{Block}_{2,2}$ design depending on the quality of physician's decision $\rho$ and the heterogeneity $\kappa$ between populations $P_1$ and $P_2$.

We see in all pictures that the relative effect in the $\text{POR}_{2,2}$ and the $\text{CUtLASS}_{2,2}$ design is positive if the quality of physicians' decisions fulfils $\rho > 0.5$. If the physician decided in more than the half of the patients cases for the not optimal treatment (i.e. $\rho < 0.5$), the relative effects become negative. Therefore, besides the main hypothesis, the other hypotheses presented in Subsection 5.4.2 are very important to assess the quality of patient-oriented decisions. If the quality of patient-oriented decisions is worse than the Block design, the results of the study can change in the wrong direction. This is one of the largest points of criticism of the CUtLASS design: We can not evaluate the results of such a trial and we do not know about the quality of the physicians decision.

chapter 6

# Discussion and outlook

In this thesis we dealt with the general properties of a new trial design, the patient-oriented randomisation design, which was developed to counter problems of 'classical' RCTs facing the high complexity of therapeutic situations due to the presence of heterogeneity of patient-drug-interactions. The heterogeneity of patient collectives in medical care makes strategy comparison with different treatments contained in each strategy especially difficult. In the patient-oriented randomisation design, the patient-oriented selection of treatment was incorporated in a RCT-like design.

We started by investigating the basic properties of the patient-oriented randomisation design to understand which consequences are to be expected due to the numbers of treatments in each strategy as well as the physician's decision within the design. We have seen that there are two main groups of two-pair combinations (informative and mixed combinations) which differ in the number of different treatments the physicians have to decide between. The informative combinations offer the opportunity to asses physicians' preferences in the treatment choice. If it is assumed that the physicians make conscious choice (i.e. no random choice) in the presence of informative combinations, a clear patient-oriented decision for one of the two treatments (in one strategy) presented in that combination can be deduced. Analysing all clear patient-oriented decisions it may be derived that the physicians prefer certain treatments over others. Moreover, the informative combinations ensure that each study treatment occurs in a known minimum number of treated patients.

Therefore, we considered the allocation probability of all treatments in each strategy in the patient-oriented randomisation design compared to the allocation probabilities in the balanced block randomisation design for two strategies and in the CUtLASS design. In contrast to the block randomisation design, the allocation probability of each treatment is not fixed a priori but depends on the physicians' decisions in the patient-oriented designs. However, the range of the allocation probabilities in the CUtLASS design is larger than that in the patient-oriented randomisation design. The minimum allocation probability in the CUtLASS design is zero, whereas the minimum allocation probability in the patient-oriented randomisation design is larger than zero. 'Hence, we are able to compute the number of patients needed to avoid poorly represented and poorly powered comparisons' (Schulz et al., 2016b). However, in case that patients are intolerant of a single treatment they have to be excluded from the study, since one treatment can not be totally deselected such as in the CUtLASS design.

Although the main focus in this thesis was on the properties of the new study design, the important question concerning the feasibility of the implementation was also dealt with. We

have a look at the implementation of the new design in the performed NeSSy study. 'Even though the study design used in [the] NeSSy [study] looks more complicated [than ordinary designs] due to the integration of a clinical decision, the study was not so inconvenient for physicians and study nurses that they had difficulty following the procedures or were unwilling to collaborate. On the contrary, the personnel feedback shows that they felt themselves—their concerns for the patient and their expertise—to be taken more seriously' (Schulz et al., 2016a). The patient-oriented randomisation design 'has been evaluated very positively by the physicians at the trial centres. Physicians found the design suitable and practical in its benefits. [...] Furthermore, patients participate more readily in the study design because they feel that their individual experience and needs are being taken into account' (Schulz et al., 2016a). The demonstrated feasibility of this new biometric design is an important result. However, the NeSSy study also pointed out that the probability of imbalances in strategies in a patient-oriented randomisation design is large because of the large minimum block length (number of two-pair combination multiplied with the number of strategies) in the randomisation list. Additional investigations assessed the probability of imbalances in strategies as well as in the two-pair combination frequencies. It turned out, that minor modifications in the randomisation list decrease the probability of imbalances without changes in the implementation of the study design.

With respect to practical application we presented a statistical model to evaluate normally distributed endpoints in an unbalanced one-way classification with fixed effects and the concept of contrasts which can be extended independent of the design used. We have seen that not only the main strategy comparison contrast is of particular interest but also hypotheses dealing with consequences from the patient-oriented decisions. 'Paradoxically, the main limitation of this design emerges from the issue it solves: it is the physician's experience and knowledge that make strategy comparison in a heterogeneous patient group possible.' (Schulz et al., 2016a) Yet patient-oriented designs such as the CUtLASS design and the patient-oriented randomisation design only work as well as the physicians selecting the treatments. In contrast to the CUtLASS design, in the patient-oriented randomisation design, it is possible to prove whether the patient-oriented choice results in a more effective treatment due to the specific random design. Therefore, we distinguished (sometimes with supplementary information from the physician) between patients receiving the treatment not only due to randomisation but due to a patient-oriented decision of the physician (patient-oriented treated patients) and patients receiving the treatment due to randomisation's reasons (randomised choice treated patients). After that we were able to test the difference in treatment means between patient-oriented treated patients and randomised choice treated patients in each treatment, each strategy, or overall. In particular, the possibility to analyse the difference between strategies for subgroups consisting of only randomised choice treated patients or only patient-oriented choice treated patients may help to test the assumptions about the heterogeneity of patient-drug-interaction in the patient-oriented randomisation design. Furthermore, we have seen that in a block randomisation design under certain conditions there is no treatment effect observable, no matter how many patients are recruited, while using a patient-oriented randomisation design would lead to observable treatment effects. The results of the CUtLASS design may go in the 'wrong' direction without one even noticing it due to the non-optimal physician's decision. Therefore, both study designs the CUtLASS design and the block design are ethically questionable if strategies are compared in presence of heterogeneity in patient-drug-interactions.

The patient-oriented randomisation design bridges the gap between methodological restrictions of evidence-based medicine and daily clinical impressions of physicians in the

presented set-up and responds to the need for a next step in evidence-based medicine, that of 'integrating individual clinical expertise with the best available external clinical evidence from systematic research'(Sackett et al., 1996).

We conclude with an outlook on potential subjects of future research based on the trial design presented in this thesis. First of all, it seems natural to expand the theory to more than two strategies. In this case, the presented formulas and theories have to be adjusted.

Furthermore, our investigations showed that the sample size calculation depends particularly on the unknown allocation of treatments' sample sizes in case of balanced strategies' sample sizes. However, the considerations from Chapter 4 on imbalances in strategies permit more extreme values of $\eta$ than we observed in Chapter 5. For large imbalances in strategies and for different modifications of the randomisation list the theory involving $\eta$ has to be adjusted.

'Additionally, the design provides the opportunity to learn more about therapeutic decisions in heterogeneous patient populations. Here, the differing individual medical histories, risk factors, and social and cultural perspectives are accounted for through analysing the documented reasons for therapeutic decisions based on these patient characteristics' (Schulz et al., 2016a). In this context, it is important to create a good case-report-form, which documents the reasons for the physician's choice systematically. Additionally, it would also be interesting to know which treatment the physician presumes the patient to be allocated to after a certain time and the reasons for the presumption.

Further research can be performed on the question of how to implement patient-oriented decisions in other study designs. One approach would be to let the physician choose the treatment most suitable in his opinion and in parallel to randomly choose a treatment and then to randomise between these two treatments. This design incorporates the patient-oriented approach and allows for treatment comparison as well as comparison between patient-oriented decision and random decision.

# APPENDIX A

# R PROGRAMS

The following **R** programs can be found on the appended CD:

### Chapter 4: Balance behaviour and practical implementation

Overview of the programs.

⟶ `00_Overview_programs.R`

Figures of frequencies of patient per centre and per two-pair combination (cf. Figures 4.3, 4.2 and 4.7).

⟶ `01_Figures_frequencies.R`

Simulation study basic program for a $\mathrm{POR}_{k,l}$ designs, which determines the strategy imbalance.

⟶ `02_Simulationstudy_basic.R`

Simulation studies with NeSSy study conditions including the same distribution of patients per centre. Results are shown in histograms of imbalances in strategies and two-pair combinations (cf. Figures 4.5, 4.6 and 4.8).

⟶ `03_Histogram_imbalances.R`

Simulation studies with NeSSy study conditions including the same distribution of patients per centre, but using a randomisation list with sub groups (modification I). The result is shown in one histogram of imbalance in strategies (cf. Figure 4.9).

⟶ `04_Histogram_strategy_imbalance_mod_I.R`

Simulation studies with NeSSy study conditions including the same distribution of patients per centre, but using a randomisation list with sub groups (modification I). The result is shown in one histogram of imbalance in two-pair combination (cf. Figure 4.10).

⟶ `05_Histogram_TPC_imbalance_mod_I.R`

Simulation studies with NeSSy study conditions including the same distribution of patients per centre, but using a randomisation list with sub groups and a Latin square (modification II). Results are shown in histograms of imbalances in strategies and two-pair combinations (cf. Figure 4.11).

$\longrightarrow$ `06_Histogram_imbalance_mod_II.R`

### Chapter 5: Statistical analysis

Sample size calculation for the NeSSy study for different $\eta$s (cf. Figure 5.2).

$\longrightarrow$ `07_Sample_size.R`

# Bibliography


Bretz, F., T. Hothorn, and P. Westfall (2010). *Multiple comparisons using R*. CRC Press.

Constantine, R. J. and R. Tandon (2007). Antipsychotics equivalent? CUtLASS renews the debate. *Curr Psychiatry 6*(2), 58–78.

Dawson, R. and P. W. Lavori (2012). Efficient design and inference for multistage randomized trials of individualized treatment policies. *Biostatistics 13*(1), 142–152.

Dmitrienko, A., A. C. Tamhane, and F. Bretz (eds.) (2009). *Multiple testing problems in pharmaceutical statistics*. CRC Press.

Gaebel, W., P. Falkai, S. Weinmann, and et al; Deutsche Gesellschaft für Psychiatrie, Psychotherapie und Nervenheilkunde (2006). *S3-Praxisleitlinien in Psychiatrie und Psychotherapie / Band. 1 Behandlungsleitlinie Schizophrenie*. Darmstadt: Steinkopf Verlag.

Genz, A. and F. Bretz (2002). Comparison of methods for the computation of multivariate t probabilities. *J Comp and Graph Stat 11*(4), 950–971.

Genz, A. and F. Bretz (2009). *Computation of multivariate normal and t probabilities*, Volume 195. Springer Science & Business Media.

Georgii, H.-O. (2009). *Stochastik: Einführung in die Wahrscheinlichkeitstheorie und Statistik*. Walter de Gruyter GmbH & Co KG.

Graybill, F. A. (1961). *An introduction to linear statistical models*. New York: McGraw-Hill.

Hallstrom, A. and K. Davis (1988). Imbalance in treatment assignments in stratified blocked randomization. *Controlled Clinical Trials 9*(4), 375–382.

Jones, P. B., T. R. Barnes, L. Davies, et al. (2006). Randomized controlled trial of the effect on Quality of Life of second-vs first-generation antipsychotic drugs in schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1). *Arch Gen Psychiatry 63*(10), 1079–1087.

Kahn, R. S., W. W. Fleischhacker, H. Boter, and et al; EUFEST study group (2008). Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. *Lancet 371*(9618), 1085–1097.

Kirk, R. E. (1995). *Experimental Design: Procedures for the Behavioral Sciences (3rd ed.)*. California: Brooks/Cole.

Kleijnen, J., P. Gotzsche, R. Kunz, et al. (1997). So what's so special about randomisation? In A. Maynard and I. Chalmers (Eds.), *Non-random Reflections on Health Services Research*, pp. 93–106. BMJ Publishing Group.

Korn, E. L. and S. Baumrind (1998). Clinician preferences and the estimation of causal treatment differences. *Statistical Science 13*(3), 209–235.

Kundt, G. (2002). *Randomisierungsverfahren für kontrollierte klinische Studien: eine Analyse ihres Balanceverhaltens und ihr Einfluß auf die Auswertung klinischer Studien mittels Permutationstests*. Shaker.

Lachin, J. M. (1988). Statistical properties of randomization in clinical trials. *Controlled Clinical Trials 9*(4), 289–311.

Lavori, P. W., R. Dawson, and A. J. Rush (2000). Flexible treatment strategies in chronic disease: clinical and research implications. *Biol Psychiatry 48*(6), 605–614.

Lei, H., I. Nahum-Shani, K. Lynch, et al. (2012). A SMART design for building individualized treatment sequences. *Annu Rev Clin Psychol 8*, 21–48.

Lieberman, J. A., T. S. Stroup, J. P. McEvoy, and et al; Clinical Antipsychotis Trials of Intervention Effectiveness (CATIE) Investigators (2005). Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Eng J Med 353*(12), 1209–1223.

Murphy, S. A. (2005). An experimental design for the development of adaptive treatment strategies. *Statistics in Medicine 24*(10), 1455–1481.

Naber, D. and M. Lambert (2009). The CATIE and CUtLASS studies in schizophrenia. *CNS Drugs 23*(8), 649–659.

O'Brien, R. and K. Muller (1993). *Applied analysis of variance in behavioral science*. New York: Marcel Decker.

Pocock, S. J. (1979). Allocation of patients to treatment in clinical trials. *Biometrics 35*(1), 183–197.

Pocock, S. J. (1982). Statistical aspects of clinical trial design. *The Statistician 31*(1), 1–18.

Pocock, S. J. and R. Simon (1975). Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics 31*(1), 103–115.

Rosenberger, W. F. and J. M. Lachin (2004). *Randomization in clinical trials: theory and practice*. John Wiley & Sons.

Sackett, D. L., W. M. C. Rosenberg, J. A. M. Gray, et al. (1996). Evidence based medicine: what it is and what it isn't. *BMJ 312*(7023), 71–72.

Scheffé, H. (1959). *The Analysis of Variance*. New York: Wiley.

Schulz, C., J. Timm, J. Cordes, et al. (2016a). Patient-oriented randomisation: A new trial design applied in the Neuroleptic Strategy Study. *Clin Trials 13*(3), 252–259.

Schulz, C., J. Timm, J. Cordes, et al. (2016b). Response from the authors. *Clin Trials 13*(3), 260–261.

Schulz, K. F. and D. A. Grimes (2002). Generation of allocation sequences in randomised trials: chance, not choice. *Lancet 359*(9305), 515–519.

Stroup, T. S., J. A. Lieberman, J. P. McEvoy, et al. (2007). Effectiveness of olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia after discontinuing perphenazine: a CATIE study. *American J Psychiatry 164*(3), 415–427.

White, S. and L. Freedman (1978). Allocation of patients to treatment groups in a controlled clinical study. *Br J Canc 37*(5), 849–857.

Winer, B. J., D. R. Brown, and K. M. Michels (1991). *Statistical principles in experimental design –3rd ed.* New York: McGraw-Hill.