

# Stage One Randomization Imbalance Simulations

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## Minimization Metrics

Let  $n_{A_{ij}}$  denote the number of patients that are on treatment A for the  $j$ -th level of prognostic factor  $i$ . Let  $n_{A_{ijs}}$  denote the number of patients that are on treatment A for the  $j$ -th level of prognostic factor  $i$  at site  $s$ .

$$n_A = \sum_{j=1}^{k_i} n_{A_{ij}}$$

Let  $\mathcal{T}$  denote the set of treatments

- Study-wide treatment imbalance:

$$\max_{a, b \neq a \in \mathcal{T}} |n_a - n_b|$$

- Study-wide prognostic factor:

$$\max_{a, b \in \mathcal{T}} |n_{a_{ij}} - n_{b_{ij}}|$$

- Within-site overall treatment imbalance:

$$\max_s \max_{a, b \in \mathcal{T}} |n_{a_s} - n_{b_s}|$$

- Within-site prognostic factor imbalance:

$$\max_s \max_{a, b \in \mathcal{T}} |n_{a_{ijs}} - n_{b_{ijs}}|$$

## Accounting for contraindications