A Confidence Interval for the Probability Difference of Overall Treatment Effect – Simulation Study

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Abstract
One of the main aims of the meta-analysis of clinical trials is the determination of the effectivity of a new type of treatment. The effectivity is determined by the difference of the effectivity of a standard treatment and the new treatment. In the case of binary data the difference can be measured by a probability difference. This paper presents the construction of the confidence interval for the probability difference of overall treatment effects in the meta-analysis based on multicentre trials. For the construction of the confidence interval the procedures of Wimmer & Witkovský (2004) and Kenward & Roger (1997) have been used. The second part of this paper is a simulation study which presents properties of the proposed confidence interval.

Keywords multicenter trial, confidence interval, probability of success, linear model with random effects.


Received: July 20, 2010; Revised: October 6, 2010; Accepted: October 7, 2010.

1 The model
Let us consider a clinical trial performed in $I$ centers. Suppose that the number of subjects included in the trial in the $i$th center is $n_{T,i} + n_{C,i}$ for $i = 1, 2, \ldots, I$ where $n_{T,i}$ is the number of patients in the treated group and $n_{C,i}$ is the number of patients in the control group. Patients in the treated group in the $i$th center succeed with probability $p_{T,i}$ and patients in the control group in the $i$th center succeed with probability $p_{C,i}$ for $i = 1, 2, \ldots, I$. All subjects are consider to be independent.

Number of successes in the treated group in the $i$th center is denoted by random variable $X_{T,i}$. Then $X_{T,i} \sim Bi(n_{T,i}, p_{T,i})$. Number of successes in the control group in the $i$th center is denoted by random variable $X_{C,i}$. Then $X_{C,i} \sim Bi(n_{C,i}, p_{C,i})$. For $l \in \{T, C\}$ number of successes in the control group in the $i$th center is denoted by random variable $X_{l,i}$. Then $X_{l,i} \sim Bi(n_{l,i}, p_{l,i})$ for $l \in \{T, C\}$ means that $X_{l,i}$ has binomial distribution with the sample of size $n_{l,i}$ and the probability of success $p_{l,i}$. Random variables $X_{T,1}, \ldots, X_{T,I}, X_{C,1}, \ldots, X_{C,I}$ are stochastic independent. We will next work with random variables.
Suppose that the true probabilities of success in the \(l\)th center \(p_{T,l}\) and \(p_{C,l}\), randomly fluctuate around common probabilities of success \(p_T\) and \(p_C\). We want to estimate the probability difference \(p_T - p_C\). So

\[
p_{l,i} = p_l + b_{l,i}, \quad \text{for } l \in \{T, C\} \text{ and } i = 1, \ldots, I. \tag{1.2}
\]

where \(b_{l,i}\) is a random effect of the \(i\)th center and suppose that \(b_{l,i} \sim N(0, \sigma^2_{l,0})\) \(^1\) which means \(b_{l,i}\) is normally distributed with the mean 0 and the variance \(\sigma^2_{l,0}\).

The final situation can be represented by linear model with random effects

\[
Y_{l,i} = p_l + b_{l,i} + \varepsilon_{l,i}, \quad \text{for } l \in \{T, C\} \text{ and } i = 1, \ldots, I. \tag{1.3}
\]

where \(\varepsilon_{l,i}\) are error terms and \(\varepsilon_{l,i} \sim N(0, \sigma^2_{l,i}/n_{l,i})\). In matrix notation we get

\[
Y = \begin{pmatrix} Y_T \\ Y_C \end{pmatrix} \approx N \left( \begin{pmatrix} I_{I \times I} \\ 0_{I \times I} \end{pmatrix}, \begin{pmatrix} p_T & 0 \\ 0 & p_C \end{pmatrix} \right), \quad \Sigma = \sigma^2_{T,0} \begin{pmatrix} I_{I \times I} & 0 \\ 0 & 0 \end{pmatrix} + \sigma^2_{C,0} \begin{pmatrix} 0 & 0 \\ 0 & I_{I \times I} \end{pmatrix} + \sum_{i=1}^{I} \sigma^2_{T,i} G_i + \sum_{j=1}^{I} \sigma^2_{C,j} H_j, \tag{1.4}
\]

where for \(i, j = 1, \ldots, I\)

\[
G_i = \begin{pmatrix} 0 & \cdots & 0 \\ \vdots & \ddots & \vdots \\ 0 & \cdots & 0 \\ 0_{I \times I} & \cdots & 0_{I \times I} \end{pmatrix}, \quad H_j = \begin{pmatrix} 0_{I \times I} & 0_{I \times I} \\ 0 & \cdots & 0 \\ \vdots & \ddots & \vdots \\ 0_{I \times I} & 0_{I \times I} \end{pmatrix}.
\]

Notation \(Y \approx N(\mu, \Sigma)\) means that \(Y\) has approximately normal distribution with mean \(\mu\) and variance matrix \(\Sigma\).

### 2 Point estimator of the vector of common probabilities of success

If we know the variance components \(\sigma^2_{l,0}\) and \(\sigma^2_{l,i}\) for \(l \in \{T, C\}\) and \(i = 1, \ldots, I\), the optimal estimator of the vector of the common probability of successful treatment would be

\[^1\text{Of course it is supposed that } \sigma^2_{l,0} \text{ is such that 'practically' } 0 < p_l + b_{l,i} < 1. \text{ In simulations it is ensured with a proper choice of } \sigma^2_{l,0}. \text{ In the case mentioned in section 4, it is } \sigma^2_{l,0} \in \left\{ 0, 1, 3 \right\}^2. \text{ The case mentioned in section 4, it is } \sigma^2_{l,0} \in \left\{ 0, \frac{1}{4} \left( \frac{p_l}{3} \right)^2, \frac{1}{4} \left( \frac{p_l}{3} \right)^2 + \frac{1}{4} \left( 1 - p_l \right)^2 \right\} \text{ for } p_l \leq 0.5 \text{ and } \sigma^2_{l,0} \in \left\{ 0, \frac{1}{4} \left( 1 - p_l \right)^2, \frac{1}{4} \left( 1 - p_l \right)^2 + \frac{1}{4} \left( 1 - p_l \right)^2 \right\} \text{ for } p_l > 0.5. \text{ The unacceptable situations happened in case of } \sigma^2_{l,0} = \frac{1}{4} \left( \frac{p_l}{3} \right)^2. \text{ In 0.14 %, } \sigma^2_{l,0} = \frac{3}{4} \left( \frac{p_l}{3} \right)^2 \text{ in 0.03 % and } \sigma^2_{l,0} = \frac{1}{2} \left( \frac{p_l}{3} \right)^2 \text{ in 0.001 % from 100000 replications.\right\}}\]
\[
\begin{pmatrix}
\hat{p}_T \\
\hat{p}_C
\end{pmatrix}
= \left( \begin{pmatrix} 1_{1 \times I} & 0_{1 \times I} \\ 0_{1 \times I} & 1_{1 \times I} \end{pmatrix} \right)
\Sigma^{-1}
\left( \begin{pmatrix} 1_{I \times 1} & 0_{I \times 1} \\ 0_{I \times 1} & 1_{I \times 1} \end{pmatrix} \right)^{-1}
\left( \begin{pmatrix} 1_{1 \times I} & 0_{1 \times I} \\ 0_{1 \times I} & 1_{1 \times I} \end{pmatrix} \right)
\Sigma^{-1}Y. \quad (2.1)
\]

So we replace unknown covariance matrix \( \Sigma \) by its estimator \( \hat{\Sigma} \) which we get if we replace the unknown variance components \( \sigma^2_{l,0} \) and \( \sigma^2_{l,i} \) by their estimators \( \hat{\sigma}^2_{l,0} \) and \( \hat{\sigma}^2_{l,i} \) for \( l \in \{T, C\} \) and \( i = 1, \ldots, I \). The estimators \( \hat{\sigma}^2_{l,0} \) and \( \hat{\sigma}^2_{l,i} \) we derive as follows.

From (1.1) we get

\[
\text{var}(Y_{l,i}) = p_{l,i}(1 - p_{l,i})
\]

and using notation from (1.3) we obtain

\[
\sigma^2_{l,i} = p_{l,i}(1 - p_{l,i})
\]

for \( l = \{T, C\} \) and \( i = 1, \ldots, I \). Now consider an estimator of \( \sigma^2_{l,i} \) which was suggested by Agresti & Caffo (2000) as

\[
\hat{\sigma}^2_{l,i} = \tilde{p}_{l,i}(1 - \tilde{p}_{l,i}), \text{ where } \tilde{p}_{l,i} = \frac{X_{l,i} + 2}{n_{l,i} + 4}.
\]

Then we can write

\[
\hat{\sigma}^2_{l,i} = \frac{X_{l,i} + 2}{n_{l,i} + 4} \left( 1 - \frac{X_{l,i} + 2}{n_{l,i} + 4} \right) \text{ for } l \in \{T, C\} \text{ and } i = 1, \ldots, I.
\]

For estimation of \( \sigma^2_{l,0} \) we use procedure suggested by Mandel & Paule (1982). The estimator \( \hat{\sigma}^2_{l,0} \) for \( l \in \{T, C\} \) we obtain as iterative solution of the following equations

\[
\hat{\mu}_{l,0}^{MP} = \frac{\sum_{i=1}^{I} X_{l,i}}{n_{l,0} + \hat{\sigma}^2_{l,i} / \hat{\sigma}^2_{l,0}}
\]

\[
\sum_{i=1}^{I} \left( \frac{X_{l,i}}{n_{l,i}} - \hat{\mu}_{l,0}^{MP} \right)^2 \hat{\sigma}^2_{l,0} + \frac{\hat{\sigma}^2_{l,i}}{n_{l,i}} = I - 1.
\]

Finally we obtain a point estimator of the vector of the common probabilities of successful treatment

\[
\hat{p} = \left( \begin{pmatrix} \hat{p}_T \\
\hat{p}_C \end{pmatrix} \right) = \left( \begin{pmatrix} \sum_{i=1}^{I} \frac{X_{T,i}}{n_{T,0} + \hat{\sigma}^2_{T,0} / \hat{\sigma}^2_{T,i}} \\
\sum_{j=1}^{J} \frac{X_{T,j}}{n_{T,0} + \hat{\sigma}^2_{T,0} / \hat{\sigma}^2_{T,j}} \\
\sum_{j=1}^{J} \frac{X_{C,i}}{n_{C,0} + \hat{\sigma}^2_{C,0} / \hat{\sigma}^2_{C,i}} \\
\sum_{j=1}^{J} \frac{X_{C,j}}{n_{C,0} + \hat{\sigma}^2_{C,0} / \hat{\sigma}^2_{C,j}} \end{pmatrix} \right). \quad (2.2)
\]
3 Interval estimator of the probability difference

As an estimation of the covariance matrix of $\hat{p}$ is commonly used

$$\Phi = \left( \begin{array}{cc} 1_{I \times I} & 0_{1 \times I} \\ 0_{1 \times I} & 1_{I \times I} \end{array} \right) \Sigma^{-1} \left( \begin{array}{cc} 1_{I \times I} & 0_{I \times I} \\ 0_{I \times I} & 1_{I \times I} \end{array} \right)^{-1}.$$  

Kenward & Roger (1997) suggested an adjusted estimator $\Phi_A$

$$\Phi_A = \Phi + 2\Lambda,$$  \hspace{1cm} (3.1)

where

$$\Lambda = \Phi \left\{ \sum_{k=1}^{2I+2} \sum_{l=1}^{2I+2} \hat{W}_{kl}(\hat{Q}_{kl} - \hat{P}_k \hat{P}_l) \right\} \Phi$$

and $\hat{W}_{kl}$ is the $(k,l)$th element of estimator of the covariance matrix of the variance components $\sigma_{l,0}^2$ and $\sigma_{l,i}^2$ for $l \in \{T, C\}$ and $i = 1, \ldots, I$. The covariance matrix $W$ can be obtained as inversion of the expected information matrix of the variance components REML estimators.

$$W(\sigma_{T,0}^2, \sigma_{T,1}^2, \ldots, \sigma_{C,0}^2, \sigma_{C,1}^2, \ldots, \sigma_{C,i}^2) = I_F^{-1}(\sigma_{T,0}^2, \sigma_{T,1}^2, \ldots, \sigma_{C,0}^2, \sigma_{C,1}^2, \ldots, \sigma_{C,i}^2).$$

Elements of $I_F$ we get from

$$\{I_F\}_{kl} = \frac{1}{2} \left[ \{S\}_{kl} - \text{Tr}(2\Phi Q_{kl} - \Phi P_k \Phi P_l) \right]$$ for $k, l \in \{1, 2, \ldots, 2I + 2\}$.

And next using Kenward & Roger’s procedure we have for $i = 1, \ldots, I$, $j = 1, \ldots, I$, $k = 1, \ldots, I$, $i \neq k$ and $j \neq k$ (in the same notation as in Kenward & Roger (1997))

$$P_{T,0} = \left( -\sum_{i=1}^{I} \left( \frac{n_{T,i}}{n_{T,0} + \sigma_{T,i}^2} \right)^2 \right) \left( \begin{array}{cc} 0 \\ 0 \end{array} \right), \quad P_{C,0} = \left( -\sum_{j=1}^{I} \left( \frac{n_{C,j}}{n_{C,0} + \sigma_{C,j}^2} \right)^2 \right) \left( \begin{array}{cc} 0 \\ 0 \end{array} \right),$$

$$P_{T,i} = \left( -\frac{n_{T,i}}{(n_{T,0} + \sigma_{T,i}^2)^2} \right) \left( \begin{array}{cc} 0 \\ 0 \end{array} \right), \quad P_{C,j} = \left( -\frac{n_{C,j}}{(n_{C,0} + \sigma_{C,j}^2)^2} \right) \left( \begin{array}{cc} 0 \\ 0 \end{array} \right),$$

$$Q_{T,0;0} = \left( \sum_{i=1}^{I} \left( \frac{n_{T,i}}{n_{T,0} + \sigma_{T,i}^2} \right)^3 \right) \left( \begin{array}{cc} 0 \\ 0 \end{array} \right), \quad Q_{C,0;0} = \left( \sum_{j=1}^{I} \left( \frac{n_{C,j}}{n_{C,0} + \sigma_{C,j}^2} \right)^3 \right) \left( \begin{array}{cc} 0 \\ 0 \end{array} \right),$$

$$Q_{T,0;1} = \left( \frac{n_{T,1}}{(n_{T,0} + \sigma_{T,1}^2)^2} \right) \left( \begin{array}{cc} 0 \\ 0 \end{array} \right), \quad Q_{C,0;1} = \left( \frac{0}{n_{C,0} + \sigma_{C,0}^2} \right) \left( \begin{array}{cc} 0 \\ 0 \end{array} \right),$$

$$Q_{T,1;0} = \left( \frac{n_{T,1}}{(n_{T,0} + \sigma_{T,1}^2)^2} \right) \left( \begin{array}{cc} 0 \\ 0 \end{array} \right), \quad Q_{C,1;0} = \left( \frac{0}{n_{C,0} + \sigma_{C,0}^2} \right) \left( \begin{array}{cc} 0 \\ 0 \end{array} \right),$$

$$Q_{T,0;C,0} = Q_{T,0;C,j} = Q_{T,1;C,0} = \left( \begin{array}{cc} 0 \\ 0 \end{array} \right),$$

$$Q_{T,1;C,k} = Q_{C,j;C,k} = Q_{T,i;C,j} = \left( \begin{array}{cc} 0 \\ 0 \end{array} \right).$$
and nonzero elements of $S$

$$\{S\}_{T,0;T,0} = \sum_{i=1}^{I} \left( \frac{n_{T,i}}{n_{T,i} \sigma_{T,i}^2 + \sigma_T^2} \right)^2, \quad \{S\}_{C,0;C,0} = \sum_{j=1}^{J} \left( \frac{n_{C,j}}{n_{C,j} \sigma_{C,0}^2 + \sigma_{C,j}^2} \right)^2,$$

$$\{S\}_{T,0;T,i} = \frac{n_{T,i}}{n_{T,i} \sigma_{T,i}^2 + \sigma_T^2}, \quad \{S\}_{C,0;C,j} = \frac{n_{C,j}}{n_{C,j} \sigma_{C,0}^2 + \sigma_{C,j}^2},$$

$$\{S\}_{T,i;T,i} = \frac{1}{n_{T,i} \sigma_{T,i}^2 + \sigma_T^2}, \quad \{S\}_{C,j;C,j} = \frac{1}{n_{C,j} \sigma_{C,0}^2 + \sigma_{C,j}^2}.$$ 

The matrices $\hat{W}$, $\hat{Q}$ and $\hat{P}$ are estimators of $W$, $Q$ and $P$ which we obtain by replacing unknown variance components $\sigma_{T,0}^2, \sigma_{T,1}^2, \ldots, \sigma_{T,I}^2, \sigma_{C,0}^2, \sigma_{C,1}^2, \ldots, \sigma_{C,I}^2$ by their estimators $\hat{\sigma}_{T,0}^2, \hat{\sigma}_{T,1}^2, \ldots, \hat{\sigma}_{T,I}^2, \hat{\sigma}_{C,0}^2, \hat{\sigma}_{C,1}^2, \ldots, \hat{\sigma}_{C,I}^2$.

Kenward & Roger (1997) also suggested an approximation of the random variable

$$\lambda F = \lambda (\hat{p}_T - \hat{p}_C - (p_T - p_C))^2 \begin{pmatrix} 1 & -1 \end{pmatrix} \begin{pmatrix} \hat{A} & 1 \end{pmatrix}^{-1}$$

by Fisher-Snedecor distribution with 1 and $m$ degrees of freedom where

$$\lambda = \frac{m}{E^*(m-2)} \quad \text{and} \quad m = 4 + \frac{3}{\rho - 1}. \quad (3.2)$$

Also in the same notation as in Kenward & Roger (1997) all necessary quantities we get as

$$\rho = \frac{V^*}{2(E^*)^2}, \quad E^* = \frac{1}{1 - A_2}, \quad V^* = \frac{1 + c_1 B}{(1 - c_2 B)^2 (1 - c_3 B)},$$

$$c_1 = \frac{g}{3 + 2(1 - g)}, \quad c_2 = \frac{1 - g}{3 + 2(1 - g)}, \quad c_3 = \frac{3 - g}{3 + 2(1 - g)},$$

$$g = \frac{2A_1 - 5A_2}{3A_2}, \quad B = \frac{1}{2} (A_1 + 6A_2), \quad \Theta = \mathbf{L}(\mathbf{L}^T \hat{\Phi} \mathbf{L})^{-1} \mathbf{L}^T, \quad \mathbf{L} = \begin{pmatrix} 1 \\ -1 \end{pmatrix},$$

$$A_1 = \sum_{k=1}^{2I+2} \sum_{l=1}^{2I+2} W_{kl} \text{Tr}(\Theta \Phi P_k \Phi) \text{Tr}(\Theta \Phi P_l \Phi),$$

$$A_2 = \sum_{k=1}^{2I+2} \sum_{l=1}^{2I+2} W_{kl} \text{Tr}(\Theta \Phi P_k \Theta \Phi P_l \Phi).$$

Finally we get the $100 \times (1 - \alpha)$ confidence interval for the difference of probabilities of overall treatment effects $p_T - p_C$ in the form

$$\left( \hat{p}_T - \hat{p}_C - \lambda^{-1} \begin{pmatrix} 1 & -1 \end{pmatrix} \hat{A} \begin{pmatrix} 1 \\ -1 \end{pmatrix} \right) F_{1,m}(\alpha),$$

$$\hat{p}_T - \hat{p}_C + \sqrt{\lambda^{-1} \left( \begin{pmatrix} 1 & -1 \end{pmatrix} \hat{A} \begin{pmatrix} 1 \\ -1 \end{pmatrix} \right) F_{1,m}(\alpha)} \cap (\alpha, \beta) \quad (3.3)$$
where $F_{1,m}(\alpha)$ is the critical $\alpha$-value of the Fisher-Snedecor distribution with 1 and $m$ degrees of freedom, $\hat{p}_T$ and $\hat{p}_C$ are given in (2.2), $\Phi_A$ is given in (3.1), $\lambda$ and $m$ can be obtained from (3.2).

4 Simulation results

The simulation study was focused on empirical coverage probabilities of the 95% interval estimator. To explore the behavior of the confidence interval for the difference of probabilities of overall treatment effects, the simulations were conducted for four main different settings. In all four settings the values of unknown parameters $I$, $n_{T,i}$ and $n_{C,i}$, $\sigma^2_{i,0}$ where $i \in \{ T,C \}$, $p_T$ and $p_C$ were following. The number of center $I \in \{ 5, 10, 15, 20 \}$, the number of subjects $n_{T,i}, n_{C,i} \in \{ 100, 50, 30, 15, 10 \}$, the variance of random effects $\sigma^2_{i,0} \in \left\{ 0, \frac{1}{4} \left( \frac{p_i}{3} \right)^2, \frac{1}{2} \left( \frac{p_i}{3} \right)^2, \frac{3}{4} \left( \frac{p_i}{3} \right)^2, \left( \frac{p_i}{3} \right)^2 \right\}$ for $p_i \leq 0.5$, $\sigma^2_{i,0} \in \left\{ 0, \frac{1}{4} \left( 1 - \frac{p_i}{3} \right)^2, \frac{1}{2} \left( 1 - \frac{p_i}{3} \right)^2, \frac{3}{4} \left( 1 - \frac{p_i}{3} \right)^2, \left( 1 - \frac{p_i}{3} \right)^2 \right\}$ for $p_i > 0.5$ and both true probabilities of success $p_T, p_C \in \{ 0.05, 0.15, \ldots, 0.85, 0.95 \}$. For each situation 5000 replications were made.

Except 95% confidence interval from (3.3) (CI) the simulations were also conducted for modified 95% confidence interval (MCI) according Wimmer & Witkovsky (2004). The modifications was made only for diagonal elements of $S$ which were replaced by following expressions for $i = 1, \ldots, I$ and $j = 1, \ldots, I$

$$\{ S \}_{T,i:T,i} = \frac{n_{T,i}}{\sigma^4_{T,i}} \left( 1 - \frac{2 \sigma^2_{T,0}}{n_{T,i} \sigma^2_{T,0} + \sigma^2_{T,i}} + \frac{n_{T,i} \sigma^4_{T,0}}{\left( n_{T,i} \sigma^2_{T,0} + \sigma^2_{T,i} \right)^2} \right),$$

$$\{ S \}_{C,j:C,j} = \frac{n_{C,j}}{\sigma^4_{C,j}} \left( 1 - \frac{2 \sigma^2_{C,0}}{n_{C,j} \sigma^2_{C,0} + \sigma^2_{C,j}} + \frac{n_{C,j} \sigma^4_{C,0}}{\left( n_{C,j} \sigma^2_{C,0} + \sigma^2_{C,j} \right)^2} \right).$$

The empirical coverage probabilities are displayed using contour lines. The dotted line is contour line matching 95% level. In all situations described below the empirical coverage probabilities of CI weren’t below the nominal 95% level. However they weren’t lower than 99.5% level, as is illustrated by the Figure 1. The white places in the graph means the empirical coverage probabilities were 1. This is mainly due to large width of CI for small numbers of subjects.

4.1 Balanced situation across the trial

In balanced situation across the trial the number of subjects in the $i$ center in treated group $n_{T,i}$ is the same as the number of subjects in the $i$ center in control group $n_{C,i}$ and is also the same as the number of subjects in the $j$ center in treated group $n_{T,j}$ and control group $n_{C,j}$ for $i = 1, \ldots, I$ and $j = 1, \ldots, I$. That is

$$n_{T,i} = n_{T,j} = n_{C,i} = n_{C,j} \text{ for } i,j = 1, \ldots, I.$$ 

For the MCI one can observe two areas with lower empirical coverage probability with cores at $p_T = 85\%$ and $p_C = 15\%$ and wise versa for $n_{T,i} = n_{C,i} = 15$ and $\sigma^2_{T,0} = \sigma^2_{C,0} = 0$. When the value of $n_{T,i}$ or $n_{C,j}$ is increased the cores move to the lower right corner and upper left corner (Figure 2). With growing value of $I$ the area around cores grow too. One can also observe that with growing $\sigma^2_{T,0}$ or $\sigma^2_{C,0}$ these areas with lower empirical coverage probability fast grow too (Figure 3). The influence of growing $I$ and $\sigma^2_{T,0}$ or $\sigma^2_{C,0}$ is approximately same in all considered situations.
I=5, n_T = n_C = 50, m_{20} = (p/3)^2/2

Figure 1: Contour lines of CI

4.2 Balanced situations across centers
In balanced situation across centers the number of subjects in the i center in treated group n_{T,i} is different from the number of subjects in the i center in control group n_{C,i}, but is the same as the number of subjects in the j center in treated group n_{T,j} for i = 1, \ldots, I and j = 1, \ldots, I. That is

\[ n_{T,i} = n_{T,j} \neq n_{C,i} = n_{C,j} \] for \( i, j = 1, \ldots, I \).

As is illustrated in Figure 4 the second simulated situation showed similar results, only cores of areas move according to the difference between \( n_{T,i} \) and \( n_{C,i} \).
In balanced situation across groups the number of subjects in the $i$ center in treated group $n_{T,i}$ is the same as the number of subjects in the $i$ center in control group $n_{C,i}$, but is different from the number of subjects in the $j$ center in treated group $n_{T,j}$ and control group $n_{C,j}$ for $i = 1, \ldots, I$ and $j = 1, \ldots, I$. That is

$$n_{T,i} \neq n_{T,j}, n_{C,i} \neq n_{C,j} \land n_{T,i} = n_{C,i} \text{ for } i, j = 1, \ldots, I.$$ 

The third situation does not have big influence on results in compare to previous situations. The results depended mainly on the highest value between $n_{T,i}$ or $n_{C,i}$ (Figure 5).

4.3 Balanced situations across groups

4.4 Unbalanced situations
can also be different from the number of subjects in the \( j \) center in treated group \( n_{T,j} \) and control group \( n_{C,j} \) for \( i = 1, \ldots, I \) and \( j = 1, \ldots, I \). As expected this situation combine results of two previous situations.

In all situations the width of CI was approximately two times the width of MCI. In further work the comparing will be extended to higher values of \( I \), because the width of CI seems to be getting smaller with growing number of centers in which is trial conducted along with the empirical coverage probability above the nominal 95% level. The reason for conducting simulations for \( \sigma^2_{C,0} = 0 \) was a possibility of comparison these results with GLMM approach mentioned in section 4.5.
4.5 Comments on GLMM approach

The standard approach to the presented problem which can be found in Whitehead (2002) is based on generalized linear mixed model (GLMM). Let us consider random variables $Z_{ij}$ which have Bernoulli distribution with success probability $p_{ij}$ for $i = 1, \ldots, I$ and $j = 1, \ldots, n_i$ ($n_i = n_{T,i} + n_{C,i}$). Suppose the following GLMM model

$$\ln \left( \frac{p_{ij}}{1 - p_{ij}} \right) = \alpha + \beta_0 i + \beta_1 U_{ij} + \nu_{1i} U_{ij}$$

(4.1)

where $U_{ij} = 0$ for the control group, $U_{ij} = 1$ for the treated group, $\nu_{1i}$ is a random effect of the $i$th center and suppose that $\nu_{1i} \sim N(0, \sigma^2_{T,0})$. In this model there is only one random effect of the treatment and no random effect for the control group, i.e. $\sigma^2_{C,0}$. The overall treatment effect is in this model measured by a log odds ratio $\beta_1$.

According to our opinion the disadvantage of this approach is its computational behavior for small numbers of subjects $n_i$ and lower probabilities. In these cases the calculation of $\beta_1$ do not converge. The greater number of centers $I$ is the greater numbers of subjects $n_i$ have to be. The comparison of the our and the GLMM approach will be subject of further work.

References


