MULTI-CENTRE CLINICAL TRIALS WITH RANDOM ENROLLMENT: THEORETICAL APPROXIMATIONS

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ABSTRACT

We consider the problem of analysing multi-centre clinical trials when the number of patients at each centre and on each treatment arm is random and follows the Poisson distribution. Theoretical approximations are made for the first two moments of the MSE's for three different estimators of treatment effect difference that are commonly used in multi-centre clinical trials. To construct these approximations, approximations are needed for the harmonic mean and negative moments of the Poisson distribution. This is achieved through the use of recurrence relations. The accuracy of the approximations for the moments of the MSE's were then validated through comparing the theoretical values to those obtained from a simulation study under two different enrollment environments.

Key Words: multi-centre clinical trials; Mean Squared Error; Poisson distribution; negative moments; harmonic mean.

1. INTRODUCTION

In this paper we consider the problem of designing and analysing the results of multi-centre clinical trials when the number of patients for both treatment arms, at the i^{th} centre follows the Poisson distribution with parameter λ_i, $i = 1 \ldots N$. This is referred to as randomised enrollment and one of its consequences is that the MSEs of the treatment estimators are random variables. The first two moments of the MSE's for the treatment estimators are of interest, and deriving theoretical approximations for these important characteristics under two different enrollment schemes constitute the main aim of the paper. A simulation study shows that the derived approximations are accurate and of practical usefulness.

The main application of our results will be important at the planning stage of a multi-centre clinical trial. Traditional sample-size and power calculations ignore any randomness in enrollment. One effect of random enrollment is to inflate the variance of the estimated CRT as compared to the deterministic enrollment case. Consequently, sample size and power will be underestimated if random enrollment is ignored. By using the theoretical approximations given in this paper, more realistic decisions can be made when multi-centre trials are planned.

The notation, models and estimators that shall be used in this paper are in accordance with those used in Dragalin et al. (1).

Assume that we have N centres, with two treatments ($j = 1, 2$), and n_{ij} patients on the j^{th} treatment in the i^{th} centre. For the time being assume that n_{ij} are fixed, meaning that (in this section alone) all randomness is attributable to the observational errors, and possibly to the randomness in the model parameters. Careful consideration is given to the case where $n_{ij} = 0$ (which has not been the case in past papers), due to the fact that in this paper we treat the n_{ij} values as random variables (see Section 2). However, we always assume that $n_{\cdot j} = \sum_{i=1}^{N} n_{ij} > 0$ for $j = 1, 2$. Thus, there is at least one patient present on both of the treatments.

Let Y_{ijk} represent the response variable for the k^{th} patient on the j^{th} treatment in the i^{th} centre, ($i = 1, \dots, N$, $j = 1, 2$ and $k = 1, \dots, n_{ij}$). Let μ_{ij} represent the true mean response for treatment j at centre i, and $\delta_i = \mu_{i2} - \mu_{i1}$ represent the true treatment effect at centre i. Numerous methods exist for combining the values of δ_i to give a single value to describe the overall treatment effect (Combined Response to Treatment or CRT, as defined by Dragalin et al. (1)). We consider in the standard way

$$\delta = \frac{1}{N} \sum_{i=1}^{N} \delta_i,$$

which is the mean treatment effect difference.

All results of the paper can be easily generalised to a general linear CRT of the form $\delta' = \sum_{i=1}^{N} \varrho_i \delta_i$, where ϱ_i are weights determined prior to the trial, and $\varrho_i \geq 0$ with $\sum_{i=1}^{N} \varrho_i = 1$.

Fixed effects models for the treatment response, in increasing order of complexity, are as follows:

$$\begin{cases} \text{Model I} & : \; Y_{ijk} = \mu + (-1)^j \tau + \epsilon_{ijk} \,, \\ \text{Model II} & : \; Y_{ijk} = \mu_i + (-1)^j \tau + \epsilon_{ijk} \,, \\ \text{Model III} & : \; Y_{ijk} = \mu_i + (-1)^j \tau_i + \epsilon_{ijk} \,. \end{cases} \tag{1}$$

In the above models the treatment effect in centre i is represented as τ_i, or τ if the effect is constant across the centres. The centre effect at centre i is μ_i, or μ if the effect is constant across the centres. The measurement error for the k^{th} patient on treatment j in centre i is ϵ_{ijk}. These errors are assumed to be independent random variables with zero mean and the same variance $\sigma^2 > 0$.

All three models are ANOVA models. In Model I treatment is the only fixed effect, Model II has centre and treatment as fixed effects, and finally, Model III is the full fixed effect model with fixed effects terms for centre, treatment and the treatment-by-centre interactions.

The true treatment effect $\delta_i = \mu_{i2} - \mu_{i1}$ will be estimated by

$$\widehat{\Delta}_i = \begin{cases} \bar{Y}_{i2.} - \bar{Y}_{i1.} & \text{if } n_{i1} > 0 \text{ and } n_{i2} > 0\,, \\ 0 & \text{if either } \; n_{i1} = 0 \text{ or } n_{i2} = 0\,. \end{cases}$$

The standard notation for summing over a subscript is applied (that is, replacing the subscript with a dot), for example $Y_{ij.} = \sum_{k=1}^{n_{ij}} Y_{ijk}$ and $n_{.j} = \sum_{i=1}^{N} n_{ij}$. The mean of a sum is denoted by the addition of a bar, e.g. $\bar{Y}_{ij.} = \frac{1}{n_{ij}} \sum_{k=1}^{n_{ij}} Y_{ijk}$.

The respective three least squared estimators of δ, for each of the models specified above are as follows

$$\widehat{\Delta}_I = \frac{Y_{.2.}}{n_{.2}} - \frac{Y_{.1.}}{n_{.1}}\,, \tag{2}$$

$$\widehat{\Delta}_{II} = \sum_{i=1}^{N} W_i \widehat{\Delta}_i\,, \tag{3}$$

$$\widehat{\Delta}_{III} = \frac{1}{N} \sum_{i=1}^{N} \widehat{\Delta}_i\,, \tag{4}$$

where the weight of the Δ_{II} (Type II) estimator, W_i, is defined as

$$W_i = \frac{n_{i2} n_{i1}/(n_{i2} + n_{i1})}{\sum_{k=1}^{N} n_{k2} n_{k1}/(n_{k2} + n_{k1})}\,. \tag{5}$$

If $n_{ij} > 0$ for fixed i and $j = 1,\,2$, we have

$$Var(\widehat{\Delta}_i) = \frac{\sigma^2}{n_{i2}} + \frac{\sigma^2}{n_{i1}}\,,$$

and so an alternative expression for W_i would be

$$W_i = \frac{1/Var(\widehat{\Delta}_i)}{\sum_{k=1}^{N} 1/Var(\widehat{\Delta}_k)}\,.$$

In the case where both treatment arms are vacant (that is, $n_{i1} = n_{i2} = 0$), we set $\frac{n_{i1} n_{i2}}{n_{i1} + n_{i2}} = 0$, resulting in $W_i = 0$. Additionally, it is clearly evident (see (5)) that $W_i = 0$ for the case where only one of the treatment arms is vacant.

When we have so-called balanced randomisation (that is, $n_{i1} = n_{i2} = n_i$), the weights become $W_i = n_i / \sum_{k=1}^{N} n_k$, this results in the Type I and Type II estimators being the same. In the so-called balanced enrollment case (additionally, all n_i are equal for all $i = 1, \ldots, N$ and $j = 1, 2$), the weights become $W_i = 1/N$; consequently, all three estimators are equivalent.

The MSE for the three fixed effect estimators (see (2) – (4)) are as follows:

$$MSE(\Delta_I) = \sigma^2 \left(\frac{1}{n_{.2}} + \frac{1}{n_{.1}} \right) + \left[\sum_{i=1}^{N} \left(\left(\frac{n_{i2}}{n_{.2}} - \frac{n_{i1}}{n_{.1}} \right) \mu_i + \left(\frac{n_{i2}}{n_{.2}} + \frac{n_{i1}}{n_{.1}} - \frac{2}{N} \right) \tau_i \right) \right]^2 ; \tag{6}$$

$$MSE(\Delta_{II}) = \sigma^2 \sum_{i=1}^{N} W_i^2 \left(\frac{1}{n_{i2}} + \frac{1}{n_{i1}} \right) + 4 \left[\sum_{i=1}^{N} \left(W_i - \frac{1}{N} \right) \tau_i \right]^2 ; \tag{7}$$

and, if $n_{ij} > 0$ for all i, j then

$$MSE(\Delta_{III}) = \frac{\sigma^2}{N^2} \sum_{i=1}^{N} \left(\frac{1}{n_{i2}} + \frac{1}{n_{i1}} \right) .$$

If one (or both) of the treatment arms are vacant (recall, that we assume $n_{.1} > 0$ and $n_{.2} > 0$), then the MSE's for the first two estimators remain unchanged (we assume that $W_i^2 / n_{ij} = 0$ if $n_{ij} = 0$). However, this is not the case with the Type III estimator, as Δ_{III} is no longer unbiased; since $\hat{\Delta}_i$ is no longer an unbiased estimator of δ_i at centre i. We must now account for this newly introduced bias.

Let I represent the set of centres for which we have $n_{i1} > 0$ and $n_{i2} > 0$. We now have

$$\begin{aligned}
MSE(\Delta_{III}) &= E(\Delta_{III} - \delta)^2 = E \left(\frac{1}{N} \sum_{i=1}^{N} \left(\hat{\Delta}_i - \delta_i \right) \right)^2 \\
&= \frac{1}{N^2} \sum_{i_1} \sum_{i_2} E(\hat{\Delta}_{i_1} - \delta_{i_1})(\hat{\Delta}_{i_2} - \delta_{i_2}) \\
&= \frac{1}{N^2} \left[\sum_{i=1}^{N} E(\hat{\Delta}_i - \delta_i)^2 + \sum_{i_1 \neq i_2} E(\hat{\Delta}_{i_1} - \delta_{i_1})(\hat{\Delta}_{i_2} - \delta_{i_2}) \right] \\
&= \frac{1}{N^2} \left[\sum_{i \epsilon I} Var \left(\hat{\Delta}_i \right) + \sum_{i_1 \notin I} \sum_{i_2 \notin I} \delta_{i_1} \delta_{i_2} \right] \\
&= \frac{1}{N^2} \left[\sum_{i \epsilon I} Var \left(\hat{\Delta}_i \right) + \left(\sum_{i \notin I} \delta_i \right)^2 \right] .
\end{aligned}$$

By definition we have $\delta_i = \mu_{i2} - \mu_{i1}$ for the Type III model, thus (see Model III in (1)) we obtain $\mu_{i1} = \mu_i - \tau_i$ and $\mu_{i2} = \mu_i + \tau_i$ implying

$$\left(\sum_{i \notin I} \delta_i \right)^2 = \left(\sum_{i \notin I} ((\mu_i + \tau_i) - (\mu_i - \tau_i)) \right)^2 = 4 \left(\sum_{i \notin I} \tau_i \right)^2 .$$

This gives

$$MSE(\Delta_{III}) \;=\; \frac{1}{N^2}\left[\sigma^2 \sum_{i\epsilon I}\left(\frac{1}{n_{i2}}+\frac{1}{n_{i1}}\right)+4\left(\sum_{i\notin I}\tau_i\right)^2\right], \tag{8}$$

$I = \{i : n_{i1} > 0 \text{ and } n_{i2} > 0\}$.

Comparisons of the MSE's (6) – (8) prove to be difficult in view of the large numbers of parameters involved in the calculations. Consequently, to reduce the number of parameters and for simplification purposes we now assume (in accordance with Dragalin et al. (1)) that the treatment-by-centre-interactions τ_i and centre effects μ_i are both independent identically distributed random variables with means $E\,\tau_i = 1$ and $E\,\mu_i = \mu$, and variances σ_τ^2 and σ_μ^2, respectively. In this case σ_τ^2 and σ_μ^2 are the variances of the treatment-by-centre interactions and the centre effects, respectively. This is the random effects model, which is of the same form as Model III in (1), except the fixed effects are now all independently identically distributed random variables (i.i..d.r.v.'s). For this model, MSE's (6) – (8) are conditional (with respect to the values that the μ_i's and τ_i's take). As shown in Dragalin et al. (1) the unconditional MSE's (denoted as $\overline{MSE}$) of the first two estimators are

$$\overline{MSE}(\Delta_I)=\sigma^2\left(\frac{1}{n_{.2}}+\frac{1}{n_{.1}}\right)+\sigma_\mu^2\sum_{i=1}^{N}\left(\frac{n_{i2}}{n_{.2}}-\frac{n_{i1}}{n_{.1}}\right)^2+\sigma_\tau^2\sum_{i=1}^{N}\left(\frac{n_{i2}}{n_{.2}}+\frac{n_{i1}}{n_{.1}}-\frac{2}{N}\right)^2, \tag{9}$$

$$\overline{MSE}(\Delta_{II}) = \sigma^2\sum_{i=1}^{N}W_i^2\left(\frac{1}{n_{i2}}+\frac{1}{n_{i1}}\right)+4\sigma_\tau^2\sum_{i=1}^{N}\left(W_i-\frac{1}{N}\right)^2. \tag{10}$$

These formulas hold irrespectively of whether the values of n_{ij} are all positive. As stated previously, we only need to assume that $n_{.1} > 0$ and $n_{.2} > 0$.

Equation (8) implies that the unconditional $\overline{MSE}$ of the third estimator is

$$\begin{aligned}\overline{MSE}(\Delta_{III}) &= \frac{1}{N^2}\left(\sigma^2\sum_{i\epsilon I}\left(\frac{1}{n_{i2}}+\frac{1}{n_{i1}}\right)+4L\left(\sigma_\tau^2+(E\,\tau)^2\right)\right)\\ &= \frac{1}{N^2}\left(\sigma^2\sum_{i\epsilon I}\left(\frac{1}{n_{i2}}+\frac{1}{n_{i1}}\right)+4L\left(\sigma_\tau^2+1\right)\right),\end{aligned} \tag{11}$$

where L represents the number of centres that have one or more vacant treatment arms.

For the case where we have all $n_{ij} > 0$, formula (11) simplifies to

$$\overline{MSE}(\Delta_{III}) = \frac{\sigma^2}{N^2}\sum_{i=1}^{N}\left(\frac{1}{n_{i2}}+\frac{1}{n_{i1}}\right),$$

which coincides with that of Dragalin et al. (1).

It can easily be seen from studying (9) – (11) (and explained in Section 6) that in order to derive theoretical estimates for the first two moments of the $\overline{MSE}$, one must first derive approximations for the first four negative moments of the Poisson distribution. Additionally, to estimate the first two moments of $\overline{MSE}(\Delta_{II})$, approximations will be required for the first four moments of the weights W_i, $i = 1 \ldots N$.

For the earlier sections of this paper we shall use the simplified notation introduced below, and will not be considering the approximations that we derive in the context of a multi-centre clinical trial problem until Section 5 and onwards. Note that throughout this paper the index k will represent a positive integer ($k = 1,\ 2,\ 3\ \ldots$) and not the k^{th} patient.

Let $Poisson(\lambda)$ denote the Poisson distribution with parameter $\lambda > 0$, and let ξ be a random variable, $\xi \sim Poisson(\lambda)$. Additionally, let ξ_+ be the so-called positive Poisson r.v. with parameter λ; that is,

$$\Pr(\xi_+ = k) = \frac{1}{1 - e^{-\lambda}} \frac{\lambda^k}{k!} e^{-\lambda}, \quad \text{for} \quad k = 1, 2 \ldots \quad .$$

The negative moments of the Poisson distribution with parameter λ are defined as the negative moments of ξ_+:

$$\mu_{-\alpha} = E\left(\frac{1}{\xi_+^{\,\alpha}}\right) = \frac{e^{-\lambda}}{1 - e^{-\lambda}} \sum_{k=1}^{\infty} \frac{\lambda^k}{k^\alpha\, k!}, \qquad \alpha = 1,\ 2,\ 3\ \ldots\ . \tag{12}$$

In Section 3 approximations are made for the first four negative moments of the Poisson distribution. The relative error of the approximations is used as the criterion by which we determine the accuracy of the approximations, where

$$Relative\, Error = \frac{Exact\ Value\ -\ Approximate\ Value}{Exact\ Value}\,.$$

A recurrence method is used to derive the first negative moment in Section 3.1, and the same methodology is applied in Section 3.2 to obtain approximations to the higher order negative moments ($\alpha = 2, 3, 4$). Note that for small λ the moments can be easily computed using the definition (12). In particular, the relative error of the following simple approximation

$$\hat{\mu}_{-\alpha} = \frac{e^{-\lambda}}{1 - e^{-\lambda}} \sum_{k=1}^{\infty} \frac{\lambda^k}{k^\alpha\, k!} \simeq \frac{e^{-\lambda}}{1 - e^{-\lambda}} \sum_{k=1}^{3\lambda+10} \frac{\lambda^k}{k^\alpha\, k!}$$

is smaller than 10^{-10} in absolute value for all $\lambda > 0$ and $\alpha \geq 1$.

Approximations for the first four moments of the harmonic mean (H) are stated in Section 4, with H being defined as

$$H = \frac{2\xi\zeta}{\xi + \zeta} \quad \text{and} \quad \xi, \zeta \sim Poisson(\lambda)\,.$$

By comparing this with the definition of the weight of the estimator, W_i (see (5)), it becomes evident that the numerator of W_i, which we shall refer to as ω_i (see (43)) is equal to $\frac{H}{2}$. This relationship is used in Section 5 to derive approximations for the first four moments of W_i.

In Section 6 the theoretical approximations for the negative moments of the Poisson distribution derived in Section 3 are expressed in a way such that they can be used in a multi-centre problem. These approximations along with the estimates for the weights, and the first four moments of the Poisson distribution are used to derive approximations for the first two moments of all three $\overline{MSE}$'s, under Scenarios I and II.

In Section 7 we determine the accuracy of our approximations for Cases I and II (defined below) by comparing the results to those obtained via a simulation study involving $500,000$ runs.

2. ENROLLMENT SCHEMES

In much literature on multi-centre trials, the simulation studies that are performed to analyse the behaviour of the estimators have pre-defined values for the allocation of the patients across the centres, see for example Gallo (2) and Jones et al. (3). However, in this paper the allocation of patients to both of the treatments over the centres will be generated through the application of two different enrollment schemes, defined as follows:

- Scenario I: n_{i1} and n_{i2} are independent; $n_{i1} \sim Poisson(\lambda_i)$ and $n_{i2} \sim Poisson(\lambda_i)$.
- Scenario II: $n_{i1} = n_{i2} = n_i$; $n_i \sim Poisson(\lambda_i)$.

The enrollment processes for Scenarios I and II follow the Poisson distribution. Recall, a random variable X has Poisson distribution with parameter λ if

$$P(X = k|\lambda) = f(k|\lambda) = \frac{e^{-\lambda}\lambda^k}{k!}, \quad k = 0, 1, 2 \ldots .$$

The mean and variance of this distribution are $E(X) = \lambda$ and $Var(X) = \lambda$.

Scenario I is an example of when the recruitment to treatments at a centre are completely independent of one another. In Scenario II the number of patients enrolled on both treatment arms are identical (that is, $n_{i1} = n_{i2} = n_i$). This phenomenon would occur in practice when the centres have been instructed to strictly maintain the equivalent number of patients on each treatment arm.

To obtain an understanding of the behaviour of the estimators in different environments, two contrasting enrollment cases are generated, namely,

- Case I: the number of centres is small, but a large number of patients have been enrolled at each centre. In our example we take $N = 10$, $n_{i1} \sim$ *Poisson* (100) and $n_{i2} \sim$ *Poisson* (100).
- Case II: the number of centres is large, but only a small number of patients have been enrolled at each centre. In our example we take $N = 100$, $n_{i1} \sim$ *Poisson* (10) and $n_{i2} \sim$ *Poisson* (10).

Both of the cases have on average a total number of 2 000 patients, with an average of 1 000 on each treatment arm in total.

3. APPROXIMATING NEGATIVE MOMENTS

The approximation of the negative moments of the Poisson distribution has independent interest and has attracted considerable attention in the literature, especially in the field of sampling. The first negative moment μ_{-1} is of particular importance. The main applications of μ_{-1} are related to the fact that if η_j are i.i.d.r.v. with variance σ^2 and the sample has random size $n \sim Poisson(\lambda)$, then the variance of the mean $(\eta_1 + \ldots + \eta_n)/n$ is $\sigma^2\mu_{-1}$. This is a standard problem, for example, in life testing, see e.g. Bartholomew (4), David and Johnson (5), Epstein and Sobel (6) – (7), Grab and Savage (8), Mendenhall (9) and Stephan (10). Tiku's approximations of negative moments $\mu_{-\alpha}$ constructed in Tiku (11) (see (22) and (29)) have been cited in a number of reference books, for instance Haight (12), Johnson et al. (13). We shall use these approximations as a benchmark for comparison in subsequent calculations.

The method used to derive approximations for μ_{-1} is based on applying a simple recurrence formula. This methodology is also applied to derive approximations for the higher order moments (these are the moments for which $\alpha > 2$ in (12)), see Section 3.2.

Denote

$$A_{l,m}(\lambda) = \sum_{x=1}^{\infty} \frac{e^{-\lambda}\lambda^x}{x^l(x+m-1)!}\,. \tag{13}$$

Thus,

$$\mu_{-\alpha} = \frac{1}{1-e^{-\lambda}} A_{\alpha,1}(\lambda)\,. \tag{14}$$

For each l, $m > 0$, we obviously have

$$\frac{1}{x^l} = \frac{1}{x^{l-1}(x+m)} + \frac{m}{x^l(x+m)}\,. \tag{15}$$

Through applying (15) to (13) we obtain the basic recurrence

$$\begin{aligned} A_{l,\,m}(\lambda) &= \sum_{x=1}^{\infty} \frac{e^{-\lambda}\lambda^{x}}{x^{l-1}(x+m)!} + \sum_{x=1}^{\infty} \frac{m e^{-\lambda}\lambda^{x}}{x^{l}(x+m)!} \\ &= A_{l-1,\,m+1}(\lambda) + m A_{l,\,m+1}(\lambda)\,, \end{aligned} \tag{16}$$

and from (13) we have

$$A_{0,m}(\lambda) = \frac{1}{\lambda^{m-1}} \left(1 - \sum_{x=0}^{m-1} \frac{e^{-\lambda}\lambda^{x}}{x!} \right) . \tag{17}$$

Note that for any fixed m,

$$A_{0,m}(\lambda) = \frac{1}{\lambda^{m-1}} + o\left(\frac{1}{\lambda^{m}}\right), \quad \text{as } \lambda \to \infty\,.$$

Through performing several iterations of the basic recurrence (16), we obtain

$$A_{l,\,m}(\lambda) = \sum_{r=0}^{N} \frac{(m+r-1)!}{(m-1)!} A_{l-1,m+r+1}(\lambda) + \frac{(m+N)!}{(m-1)!} A_{l-1,m+N+2}(\lambda)\,. \tag{18}$$

Let $B_{l,m}(\lambda)$ be the large sample approximations for $A_{l,m}(\lambda)$ that satisfy the recurrence in (18), that is,

$$B_{l,m}(\lambda) = \sum_{r=0}^{N} \frac{(m+r-1)!}{(m-1)!} B_{l-1,m+r+1}(\lambda) + \frac{(m+N)!}{(m-1)!} B_{l-1,m+N+2}(\lambda)\,, \tag{19}$$

with similar initial conditions to (17) but excluding the exponential terms:

$$B_{0,m}(\lambda) = \frac{1}{\lambda^{m-1}}\,. \tag{20}$$

In our approximations we shall ignore the last term in (19), which gives

$$B_{l,m}(\lambda) \simeq \sum_{r=0}^{N} \frac{(m+r-1)!}{(m-1)!} B_{l-1,m+r+1}(\lambda)\,. \tag{21}$$

3.1 FIRST NEGATIVE MOMENT

In this section, approximations for the first negative moment are derived. As stated earlier, Tiku's well-known approximations (see Equation (11), in Tiku (11)) will be used as a benchmark for comparison. They are defined as follows:

$$T_j^{(1)} = E\left(\frac{1}{\xi_+}\right) \simeq \frac{\left(1 + \sum_{r=3}^{j} \beta_r\right)}{(\lambda-1)(1-e^{-\lambda})}\,, \tag{22}$$

where $\beta_r = a^{(r)}/\lambda(\lambda+1)(\lambda+2)\dots(\lambda+r-1),\ r = 3,4,5,\dots$. The first four non-zero coefficients $a^{(r)}$ are: $a^{(3)} = 1,\ a^{(4)} = 7,\ a^{(5)} = 43,\ a^{(6)} = 271$.

The suggested approximations (particular cases of the approximation (25)) are more accurate than Tiku's approximations (if λ is not too small), as illustrated in Figure I.

In view of (14), to approximate μ_{-1}, approximations are needed for both $A_{1,1}(\lambda)$ and its approximation $B_{1,1}(\lambda)$. To find $A_{1,1}(\lambda)$ using (18) with $m = l = 1$ and (17), we obtain

$$\begin{aligned} A_{1,1}(\lambda) &= \sum_{r=0}^{k} r!A_{0,r+2}(\lambda) + (k+1)!A_{0,k+3}(\lambda) \\ &= \sum_{r=0}^{k} \frac{r!}{\lambda^{r+1}} \left(1 - \sum_{x=0}^{r} \frac{e^{-\lambda}\lambda^x}{x!}\right) + (k+1)!A_{0,k+3}(\lambda)\,. \end{aligned} \tag{23}$$

Similarly, using (19) and (20) we have

$$B_{1,1}(\lambda) = \frac{1}{\lambda} + \frac{1}{\lambda^2} + \frac{2}{\lambda^3} + \dots = \sum_{r=0}^{k} \frac{r!}{\lambda^{r+1}} + (k+1)!B_{0,k+3}(\lambda)\,. \tag{24}$$

To construct k^{th} order approximations for μ_{-1}, we keep the first k terms in (23) and (24), and ignore $A_{0,k+3}(\lambda)$ and $B_{0,k+3}(\lambda)$, respectively. In this way we obtain

$$\bar{\mu}_{-1}^{(k)} = \frac{1}{1-e^{-\lambda}} \sum_{r=0}^{k-1} \frac{r!}{\lambda^{r+1}} \left(1 - \sum_{x=0}^{r} \frac{e^{-\lambda}\lambda^x}{x!}\right) \simeq \frac{1}{1-e^{-\lambda}} A_{1,1}(\lambda) = \mu_{-1}$$

and

$$\hat{\mu}_{-1}^{(k)} = \sum_{r=0}^{k-1} \frac{r!}{\lambda^{r+1}} \simeq B_{1,1}(\lambda)\,. \tag{25}$$

Note that $\bar{\mu}_{-1}^{(k)} < \hat{\mu}_{-1}^{(k)}$ and $\bar{\mu}_{-1}^{(k)} < \mu_{-1}$, for all λ and k. It is not always true that $\hat{\mu}_{-1}^{(k)} < \mu_{-1}$. For small values of k and large λ, we have

$$\frac{e^{-\lambda}}{1-e^{-\lambda}} \sum_{x=0}^{k} \frac{\lambda^x}{x!} \approx 0\,, \tag{26}$$

and the respective approximation $\hat{\mu}_{-1}^{(k)}$ is smaller than μ_{-1}. However, as soon as k becomes larger, (26) no longer holds; consequently we can have $\hat{\mu}_{-1}^{(k)} > \mu_{-1}$. Hence, for small k, we always have

$$\bar{\mu}_{-1}^{(k)} < \hat{\mu}_{-1}^{(k)} < \mu_{-1}\,, \tag{27}$$

meaning that $\bar{\mu}_{-1}^{(k)}$ and $\hat{\mu}_{-1}^{(k)}$ are always smaller than μ_{-1}, with $\hat{\mu}_{-1}^{(k)}$ being more precise.

Analytical results show that when $k = \lceil 0.5\lambda \rceil$, the inequalities (27) hold for all $\lambda \geq 4$ (here, for any a, $\lceil a \rceil$ denotes the smallest integer that is greater than or equal to a). On the other hand, $\hat{\mu}_{-1}^{(k)}$ with $k = \lceil \lambda \rceil$ is always larger than μ_{-1}, but is still very precise. This implies that any $\hat{\mu}_{-1}^{(k)}$, with $\lceil \frac{\lambda}{2} \rceil \leq k \leq \lceil \lambda \rceil$, provides an extremely accurate approximation.

We studied the accuracy of two simple approximations $\hat{\mu}_{-1}^{(3)}$ and $\hat{\mu}_{-1}^{(4)}$ as compared against Tiku's approximations $T_k^{(1)}$ defined in (22). The approximation $\hat{\mu}_{-1}^{(4)}$ is expressed as

$$\hat{\mu}_{-1}^{(4)} = \frac{1}{\lambda} + \frac{1}{\lambda^2} + \frac{2}{\lambda^3} + \frac{6}{\lambda^4}\,. \tag{28}$$

In Figure I we restrict ourselves to the $T_6^{(1)}$ version of this approximation.

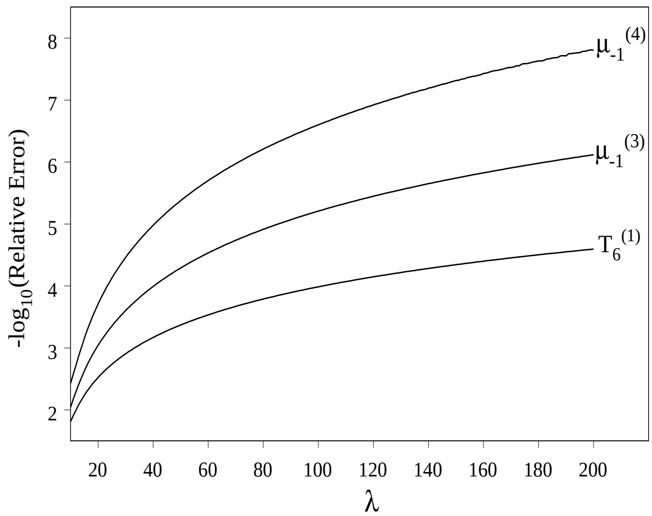

Figure I: Comparisons of -$\log_{10}$(Relative Error) of the approximations for the first negative moment verus λ. High values for $-\log$(Relative Error) indicate accurate approximations.

For values of $\lambda > 8$ we find that the approximations $\hat{\mu}_{-1}^{(3)}$, and especially $\hat{\mu}_{-1}^{(4)}$, are very accurate, comparing favorably to the more complex approximations of Tiku. Additionally, and not included in the figure, for $\lambda \geq 8$ the simpler approximations $\hat{\mu}_{-1}^{(k)}$ are marginally better than the respective approximations $\bar{\mu}_{-1}^{(k)}$.

3.2 APPROXIMATING HIGHER ORDER MOMENTS USING RECURRENCE FORMULAS

The approximations for the higher order moments will be compared against Tiku's approximations $T^{(\alpha)}$, which are defined as (see Equation (14) in Tiku (11))

$$T^{(\alpha)} = \frac{1}{(\lambda-1)(\lambda-2)\ldots(\lambda-\alpha)} \qquad \text{for } \alpha \geq 2. \tag{29}$$

Similar to the case of the first negative moment, to approximate the higher order negative moments with integer α, we must estimate either $A_{\alpha,1}(\lambda)$, or $B_{\alpha,1}(\lambda)$. Consideration will only be given to the approximations related to $B_{\alpha,1}(\lambda)$, as these approximations are simpler due to the omission of exponential terms. Additionally, for large λ and small k these approximations are again better than the more complex approximations based on the use of $A_{l,m}(\lambda)$. In the approximations that follow we will need the so-called *signless Stirling numbers of the first kind*.

		j								
	s(n,j)	1	2	3	4	5	6	7	8	9
	1	1	0	0	0	0	0	0	0	0
	2	1	1	0	0	0	0	0	0	0
	3	2	3	1	0	0	0	0	0	0
n	4	6	11	6	1	0	0	0	0	0
	5	24	50	35	10	1	0	0	0	0
	6	120	274	225	85	15	1	0	0	0
	7	720	1 764	1 624	735	175	21	1	0	0
	8	5 040	13 068	13 132	6 769	1 960	322	28	1	0
	9	40 320	109 584	118 124	67 284	22 449	4 536	546	36	1

Table I: Values for signless Stirling numbers of the first kind for $n,\, j \leq 9$.

Signless Stirling numbers of the first kind

Denote the signless Stirling number of the first kind as $s(n,\, j)$; see Polya et al. (14) and Stanley (15). These numbers satisfy the recurrence

$$s(n,\, j) = (n-1)s(n-1,\, j) + s(n-1,\, j-1), \quad n,\, j \geq 1\,,$$

with the initial conditions $s(n,\, j) = 0$ if $n \leq 0$ or $j \leq 0$, except $s(0,\, 0) = 1$. Values for these numbers where $n,\, j \leq 9$ can be seen in Table I.

We shall need the following properties of these Stirling numbers, $s(n,j)$. Let $H_n = 1 + \frac{1}{2} + \ldots + \frac{1}{n}$ denote the harmonic number. It can be shown (see Comtet (16)), that $s(n,j) = 0$ for $n < j$ and for all $n \geq j-1$

$$s(n+1,1) \quad = \quad n!\,; \tag{30}$$

$$s(n+1,2) \quad = \quad n!\left(1 + \frac{1}{2} + \ldots + \frac{1}{n}\right) = n!H_n\,; \tag{31}$$

Approximating the second negative moment

Using (21) with $l = 2$ and $m = 1$, we obtain

$$\mu_{-2} \simeq \sum_{r=0}^{N} r! B_{1,r+2}(\lambda) \,. \tag{32}$$

We construct approximations of the form

$$\mu_{-2} \simeq \mu_{-2}^{(k)} = \sum_{r=0}^{k-1} \frac{a_r}{\lambda^{r+1}} \,,$$

which we obtain from (32) with N large enough, by the repeated application of the approximations in (21), and keeping all the terms that contribute to the coefficients a_r's for $r \leq k-1$. The exact value of N in (21) and (32) is not of interest, we only require that N is large enough.

Thus, we write the "$\sum_{r=0}^{N}$" in (21) and (32) as "$\sum_{r\geq 0}$" obtaining

$$\mu_{-2} \simeq \sum_{r\geq 0} r! B_{1,r+2}(\lambda) = \sum_{r\geq 0} r! \sum_{s\geq 0} \frac{1}{\lambda^{s+r+2}} \frac{(s+r+1)!}{(r+1)!} = \sum_{r\geq 0} \frac{1}{r+1} \sum_{s\geq 0} \frac{1}{\lambda^{s+r+2}} (s+r+1)! \,.$$

Let $t = r + s + 1$. Using (31) we obtain

$$\mu_{-2} \simeq \sum_{r\geq 0} \sum_{t\geq r+1} \frac{t!}{(r+1)\lambda^{t+1}} = \sum_{t\geq 1} \frac{t!}{\lambda^{t+1}} \sum_{r=0}^{t-1} \frac{1}{r+1} = \sum_{t\geq 1} \frac{t! H_t}{\lambda^{t+1}} = \sum_{t\geq 0} \frac{s(t+1,2)}{\lambda^{t+1}} \,. \tag{33}$$

The k^{th} order approximation $\hat{\mu}_{-2}^{(k)}$ is obtained when we keep the first k terms in the right-hand side of (33), that is,

$$\mu_{-2} \simeq \hat{\mu}_{-2}^{(k)} = \sum_{t=0}^{k-1} \frac{s(t+1,2)}{\lambda^{t+1}} = \frac{1}{\lambda^2} + \frac{3}{\lambda^3} + \ldots + \frac{s(k,2)}{\lambda^k} \,. \tag{34}$$

Analytical calculations reveal that $\hat{\mu}_{-2}^{\lceil 0.5\lambda \rceil +1}$ and $\hat{\mu}_{-2}^{\lceil \lambda \rceil +1}$ compare very favorable against Tiku's approximation $T^{(2)}$. We find that $\hat{\mu}_{-2}^{\lceil \lambda \rceil +1}$ is larger than μ_{-2}, whereas $\hat{\mu}_{-2}^{\lceil 0.5\lambda \rceil +1}$ is smaller than μ_{-2}; this suggests that any $\hat{\mu}_{-2}^{(k)}$ with $\lceil \frac{\lambda}{2} \rceil + 1 \leq k \leq \lceil \lambda \rceil + 1$ would provide an extremely accurate approximation.

We discover in Figure II that the simple approximations $\hat{\mu}_{-2}^{(6)}$ and in particular

$$\hat{\mu}_{-2}^{(8)} \quad = \quad \frac{1}{\lambda^2} + \frac{3}{\lambda^3} + \ldots + \frac{13\,068}{\lambda^8} \,, \tag{35}$$

are very accurate approximations of the second negative moment.

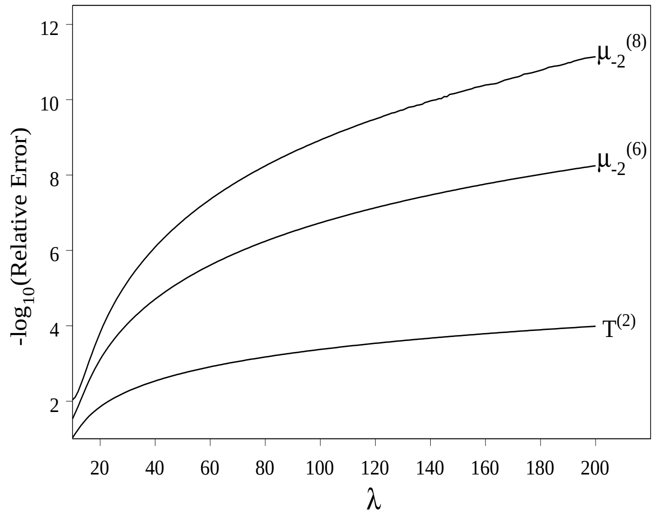

Figure II: Comparisons of -$\log_{10}$(Relative Error) of the approximations for the second negative moment versus λ.

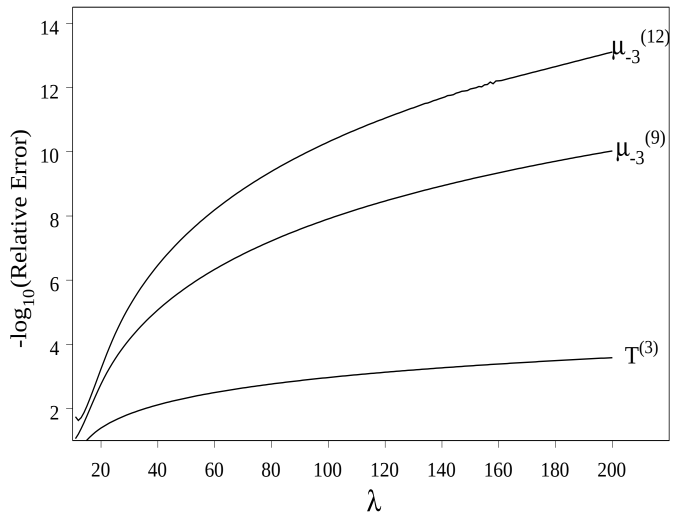

Figure III: Comparisons of -$\log_{10}$(Relative Error) of the approximations for the third negative moment versus λ.

Approximating the third and fourth negative moment

Similarly, it can be shown that the k^{th} order approximations of $\hat{\mu}_{-3}^{(k)}$ can be expressed as

$$\hat{\mu}_{-3}^{(k)} = \sum_{u=0}^{k-1} \frac{s(u+1,3)}{\lambda^{u+1}} = \sum_{u=3}^{k} \frac{s(u,3)}{\lambda^{u}} . \tag{36}$$

Analytically we discover that all of our approximations compare favorably against Tiku's approximation $T^{(3)}$, and any $\hat{\mu}_{-3}^{(k)}$ with $\lceil 0.5\lambda \rceil + 2 \leq k \leq \lceil \lambda \rceil + 2$ provides an extremely accurate approximation of μ_{-3}.

In Figure III we find that the simple approximation $\mu_{-3}^{(9)}$ and

$$\hat{\mu}_{-3}^{(12)} = \frac{1}{\lambda^3} + \ldots + \frac{118\,124}{\lambda^9} + \frac{1\,172\,700}{\lambda^{10}} + \frac{12\,753\,576}{\lambda^{11}} + \frac{120\,543\,840}{\lambda^{12}} . \tag{37}$$

provide accurate approximations for the third negative moment, particularly for larger values of λ.

The approximation for the fourth negative moment is found to be

$$\hat{\mu}_{-4}^{(k)} = \sum_{u=0}^{k-1} \frac{s(u+1,4)}{\lambda^{u+1}} = \sum_{u=4}^{k} \frac{s(u,4)}{\lambda^{u}} . \tag{38}$$

As examples, through applying the general formula (38) we obtain the following two approximations for μ_{-4}: $\hat{\mu}_{-4}^{(12)}$ and

$$\hat{\mu}_{-4}^{(16)} = \sum_{u=4}^{16} \frac{s(u,4)}{\lambda^{u}} = \frac{1}{\lambda^4} + \ldots + \frac{5\,056\,995\,703\,824}{\lambda^{16}} . \tag{39}$$

We find from Figure IV that both of these approximations for the fourth negative moment (particularly the latter) are very accurate for $\lambda > 20$.

Analogously, the k^{th} order approximation for the l^{th} order negative moment is expressed as follows:

$$\mu_{-l} \simeq \hat{\mu}_{-l}^{(k)} = \sum_{u=0}^{k-1} \frac{s(u+1,l)}{\lambda^{u+1}} = \sum_{u=l}^{k} \frac{s(u,l)}{\lambda^{u}} . \tag{40}$$

By studying Figure I it is evident that the newly derived approximations for the first negative moment compare favourably against the existing Tiku approximations. The approximations prove to be very accurate for values of $\lambda > 8$, with $\hat{\mu}_{-1}^{(4)}$ having a relative error less than 0.01.

For the higher order moments it was found (not proven) that as with the first negative moment, the simpler approximations of the form $\hat{\mu}_{-\alpha}^{(k)}$ were marginally more accurate than $\bar{\mu}_{-\alpha}^{(k)}$ approximations (for $\alpha = 2, 3$ and 4). Consequently, all the approximations presented in this paper are of the simpler variety.

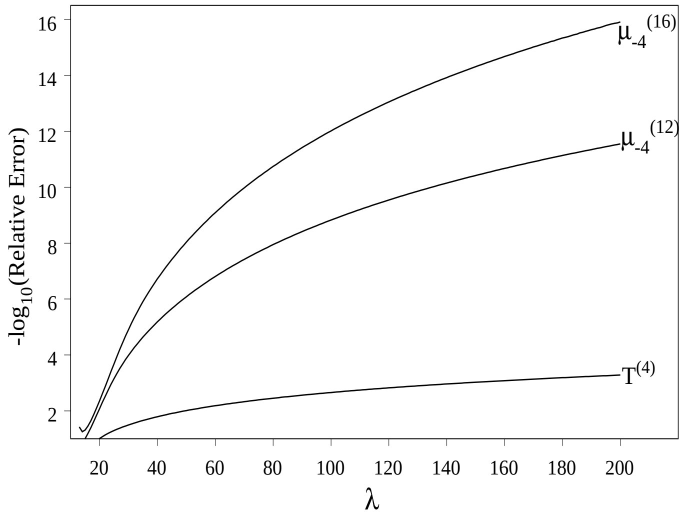

Figure IV: Comparisons of -$\log_{10}$(Relative Error) of the approximations for the fourth negative moment versus λ.

By analysing Figures II, III and IV we discover that the approximations become more accurate as the order of the negative moments increases. It is also evident that the approximations for the higher order negative moments are less accurate for smaller values of λ than the approximations for the first negative moment. The approximations for the higher order moments are accurate (that is, they have a relative error < 0.01) for $\lambda > 20$. However, it is clearly evident that the approximations compare very favorably with Tiku's existing approximations for higher order negative moments (defined in (29)).

Hence, through looking at the Figures we find that the best approximations studied would be as follows:

- First Negative Moment: $\hat{\mu}_{-1}^{(4)}$, defined in (28).
- Second Negative Moment: $\hat{\mu}_{-2}^{(8)}$, defined in (35).
- Third Negative Moment: $\hat{\mu}_{-3}^{(12)}$, defined in (37).
- Fourth Negative Moment: $\hat{\mu}_{-4}^{(16)}$, defined in (39).

These approximations are subsequently used in Section 6 to aid in the estimation of the first two moments of $\overline{MSE}\,(\Delta_I)$, $\overline{MSE}\,(\Delta_{II})$ and $\overline{MSE}\,(\Delta_{III})$.

4. APPROXIMATING THE MOMENTS OF THE HARMONIC MEAN

Let ξ and ζ be i.i.d.r.v., $\xi, \zeta \sim Poisson(\lambda)$. Set

$$H = \frac{2\xi\zeta}{\xi+\zeta} = \frac{2}{1/\xi + 1/\zeta} , \tag{41}$$

to be the harmonic mean of ξ and ζ. Jones (17) demonstrates through the use of asymptotic expansions (as $\lambda \to \infty$) that

$$\begin{aligned}
E\left(\frac{2\xi\zeta}{\xi+\zeta}\right) &= \lambda - \frac{1}{2} + O\left(\frac{1}{\lambda^{40}}\right) ; \\
E\left(\frac{2\xi\zeta}{\xi+\zeta}\right)^2 &= \lambda^2 - \frac{\lambda}{2} + \frac{3}{4} - \frac{1}{4\lambda} - \frac{1}{8\lambda^2} + O\left(\frac{1}{\lambda^3}\right) ; \\
E\left(\frac{2\xi\zeta}{\xi+\zeta}\right)^3 &= \lambda^3 + \frac{7\lambda}{4} - \frac{21}{8} + \frac{15}{8\lambda} + \frac{7}{16\lambda^2} + O\left(\frac{1}{\lambda^3}\right) ; \\
E\left(\frac{2\xi\zeta}{\xi+\zeta}\right)^4 &= \lambda^4 + \lambda^3 + \frac{13\lambda^2}{4} - \frac{57\lambda}{8} + \frac{225}{16} - \frac{121}{8\lambda} + \frac{13}{8\lambda^2} + O\left(\frac{1}{\lambda^3}\right) .
\end{aligned}$$

Thus, we can use the following approximations for the first four moments of the harmonic mean $H = 2\xi\zeta/(\xi+\zeta)$:

$$\begin{cases}
E(H) \simeq h_1 = \lambda - \frac{1}{2} ; \\
E(H^2) \simeq h_2 = \lambda^2 - \frac{\lambda}{2} + \frac{3}{4} ; \\
E(H^3) \simeq h_3 = \lambda^3 + \frac{7}{4}\lambda - \frac{21}{8} ; \\
E(H^4) \simeq h_4 = \lambda^4 + \lambda^3 + \frac{13}{4}\lambda^2 - \frac{57}{8}\lambda + \frac{225}{16} .
\end{cases} \tag{42}$$

λ	h_1	h_2	h_3	h_4
10	2.5031 10^{-7}	-2.7617 10^{-4}	1.8860 10^{-4}	1.3331 10^{-4}
15	2.7586 10^{-10}	-7.9107 10^{-5}	3.7366 10^{-5}	-1.8299 10^{-5}
25	5.8163 10^{-16}	-1.6647 10^{-5}	4.8328 10^{-6}	-1.4754 10^{-6}
50	3.5267 10^{-30}	-2.0402 10^{-6}	3.0121 10^{-7}	-4.7286 10^{-8}
100	1.8177 10^{-58}	-2.5251 10^{-7}	1.8791 10^{-8}	-1.4954 10^{-9}
200	6.7957 10^{-115}	-3.1406 10^{-8}	1.1173 10^{-9}	-4.7001 10^{-11}

Table II: Relative errors for the approximations (see (42)) of the first four moments of H against different values of λ.

By studying Table II we find that the approximations for the first four moments of the harmonic mean are extremely accurate for $\lambda > 10$. This is especially the case for the first moment of h_1, with the relative error being very small when $\lambda = 10$, and becoming minuscule for $\lambda > 25$.

5. APPROXIMATING THE MOMENTS OF W_i

Approximations are made for the first four moments of W_i by considering the numerator and denominator of $(W_i)^k$ ($k = 1, 2, 3$, and 4) as separate functions.

Scenario I: Independent $\mathbf{n_{i1}}$ and $\mathbf{n_{i2}}$

Denote

$$\omega_i = \frac{n_{i2} n_{i1}}{n_{i2} + n_{i1}} \,, \qquad \text{for independent} \quad n_{i2}, n_{i1} \sim Poisson(\lambda_i) \,, \tag{43}$$

and

$$\omega \;=\; \sum_{j=1}^{N} \omega_j \,. \tag{44}$$

From the definition for W_i (see (5)), we have $W_i = \omega_i / \omega$. Using the fact that $\omega_i = H/2$, the approximations in (42) gives the following approximations:

$$E\,\omega_i \;\simeq\; \frac{\lambda_i}{2} - \frac{1}{4} \,; \tag{45}$$

$$E\,\omega_i^2 \;\simeq\; \frac{\lambda_i^2}{4} - \frac{\lambda_i}{8} + \frac{3}{16} \,; \tag{46}$$

$$E\,\omega_i^3 \;\simeq\; \frac{\lambda_i^3}{8} + \frac{7\lambda_i}{32} - \frac{21}{64} \,; \tag{47}$$

$$E\,\omega_i^4 \;\simeq\; \frac{\lambda_i^4}{16} + \frac{\lambda_i^3}{16} + \frac{13\lambda_i^2}{64} - \frac{57\lambda_i}{128} + \frac{225}{256} \,; \tag{48}$$

$$E\,\omega \;\simeq\; \sum_{i=1}^{N} \left(\frac{\lambda_i}{2} - \frac{1}{4} \right) \,. \tag{49}$$

As $E(\omega)$ is typically large, we can use the following approximation:

$$E\left(\frac{1}{\omega}\right)^k \simeq \frac{1}{E(\omega^k)} \qquad\qquad k = 1,\, 2,\, 3,\, 4\,. \tag{50}$$

Also, since N is large, through using the asymptotic independence of ω_i and $\omega = \sum_{j=1}^{N} \omega_j$, we can state that

$$E\left(\frac{\omega_i}{\omega}\right)^k \simeq E\,\omega_i^k\, E\,\frac{1}{\omega^k} \,,\; k = 1,\, 2,\, 3,\, 4\,, \tag{51}$$

and in addition, using (50) and (51), we get

$$E\left(\frac{\omega_i}{\omega}\right)^k \;\simeq\; \frac{E\,\omega_i^k}{E\,\omega^k} \,. \tag{52}$$

To derive the second moment of ω we must use (45) and (46) to obtain

$$\begin{aligned}
\omega^2 &= \sum_{i=1}^{N}\sum_{j=1}^{N} \omega_i \omega_j \\
E\,\omega^2 &= \sum_{i,j}^{N} E(\omega_i\omega_j) = \sum_{i=1}^{N} E\,\omega_i^2 + \sum_{i=1}^{N}\sum_{j\neq i}^{N} E\,\omega_i\,E\,\omega_j \\
&= \sum_{i=1}^{N} E\,\omega_i^2 + \sum_{i=1}^{N}\sum_{j=1}^{N} E\,\omega_i\,E\,\omega_j - \sum_{i=1}^{N} (E\,\omega_i)^2 \\
&\simeq \sum_{i=1}^{N}\left(\frac{\lambda_i^2}{4} - \frac{\lambda_i}{8} + \frac{3}{16}\right) + \left[\sum_{i=1}^{N}\left(\frac{\lambda_i}{2} - \frac{1}{4}\right)\right]^2 - \sum_{i=1}^{N}\left(\frac{\lambda_i}{2} - \frac{1}{4}\right)^2 \\
&\simeq \frac{1}{4}\left[\sum_{i=1}^{N}\left(\lambda_i - \frac{1}{2}\right)\right]^2 + \frac{1}{8}\sum_{i=1}^{N}(\lambda_i + 1)\ . \qquad (53)
\end{aligned}$$

Applying similar methodology (see the Appendix for detailed calculations), we find that the approximations for the third and fourth moments of ω are

$$E\,\omega_3 \simeq \frac{1}{8}\left[\sum_{i=1}^{N}\left(\lambda_i - \frac{1}{2}\right)\right]^3 + \frac{3}{2}\sum_{i=1}^{N}\left(\frac{\lambda_i}{8} + \frac{1}{8}\right)\sum_{j=1}^{N}\left(\lambda_j - \frac{1}{2}\right) + \frac{1}{32}\sum_{i=1}^{N}(\lambda_i - 7)\,; \qquad (54)$$

$$\begin{aligned}
E\,\omega_4 \simeq{}& \frac{1}{16}\left[\sum_{i=1}^{N}\left(\lambda_i - \frac{1}{2}\right)\right]^4 + \frac{1}{4}\sum_{i=1}^{N}\left(\frac{3\lambda_i^2}{2} + \lambda_i - \frac{5}{2}\right)\sum_{j=1}^{N}\left(\lambda_j - \frac{1}{2}\right) - \frac{3}{16}\left[\sum_{i=1}^{N}\left(\lambda_i - \frac{1}{2}\right)^2\right]^2 \\
&+ \frac{3}{16}\left[\sum_{i=1}^{N}\left(\lambda_i^2 - \frac{\lambda_i}{2} + \frac{3}{4}\right)\right]^2 - \frac{1}{8}\sum_{i=1}^{N}\left(3\lambda_i^3 - \frac{49\lambda_i}{16} - \frac{15}{4}\right)\ . \qquad (55)
\end{aligned}$$

Scenario II: Dependent recruitment, $n_{i1} = n_{i2}$

In Scenario II, due to the number of patients on both treatment arms being identical, the suffix j ($j = 1, 2$) used to denote the treatment arm is omitted. Thus, we have $n_{i2} = n_{i1} = n_i$ and $n_. = \sum_{i=1}^{N} n_i$.

For the remainder of the paper all estimators associated with Scenario II will be represented with the addition of an asterisk, *. The weights W_i ($i = 1 \ldots N$) must now be re-defined. Denote

$$\omega_i^* = \frac{n_i}{2} \ \text{ for } n_i \sim Poisson(\lambda_i)\,, \qquad (56)$$

and

$$\omega^* = \sum_{j=1}^{N} \omega_j^* = \frac{n_.}{2}\,. \qquad (57)$$

Hence,

$$E\,\omega_i^* = \frac{\lambda_i}{2}\ ; \tag{58}$$

$$E\,\omega_i^{*\,2} = \frac{\lambda_i + \lambda_i^2}{4}\ ; \tag{59}$$

$$E\,\omega_i^{*\,3} = \frac{\lambda_i + 3\lambda_i^2 + \lambda_i^3}{8}\ ; \tag{60}$$

$$E\,\omega_i^{*\,4} = \frac{\lambda_i + 7\lambda_i^2 + 6\lambda_i^3 + \lambda_i^4}{16}\ ; \tag{61}$$

$$E\,\omega^* = \frac{1}{2}\sum_{i=1}^{N}\lambda_i\ . \tag{62}$$

Using the fact that, $\omega^* \sim \ Poisson\left(\frac{1}{2}\sum_{i=1}^{N}\lambda_i\right)$, and denoting $\Lambda = \sum_{i=1}^{N}\lambda_i$, we find the second, third and fourth moments of ω^*:

$$E\,\omega^{*\,2} = \frac{1}{4}\left[\Lambda + \Lambda^2\right]\ ; \tag{63}$$

$$E\,\omega^{*\,3} = \frac{1}{8}\left[\Lambda + 3\Lambda^2 + \Lambda^3\right]\ ; \tag{64}$$

$$E\,\omega^{*\,4} = \frac{1}{16}\left[\Lambda + 7\Lambda^2 + 6\Lambda^3 + \Lambda^4\right]\ . \tag{65}$$

6. APPROXIMATING THE FIRST TWO MOMENTS OF $\overline{MSE}\,(\Delta_I) - \overline{MSE}\,(\Delta_{III})$

For the approximations in this section, we will need the approximations for the first four moments of W_i derived in Section 5, the approximations for the first four negative moments of the Poisson distribution (see Section 3), and finally the first four moments of the Poisson distribution, which are by definition

$$\begin{cases} E\,n_{i1} = E\,n_{i2} = \lambda_i\,; \\ E\,n_{i1}^2 = E\,n_{i2}^2 = \lambda_i + \lambda_i^2\,; \\ E\,n_{i2}^3 = E\,n_{i2}^3 = \lambda_i + 3\lambda_i^2 + \lambda_i^3\,; \\ E\,n_{i1}^4 = E\,n_{i2}^4 = \lambda_i + 7\lambda_i^2 + 6\lambda_i^3 + \lambda_i^4\ . \end{cases} \tag{66}$$

To alter the notation such that it is applicable in the context of a multi-centre trial problem, we shall denote the approximations for the negative moments as follows:

$$\Upsilon_{i,\alpha} \simeq E\,\frac{1}{{n_{i1}}^{\alpha}} = E\,\frac{1}{{n_{i2}}^{\alpha}}\ , \quad \alpha = 1,\,2\ ; \tag{67}$$

$$\Upsilon_{\alpha} \simeq E\,\frac{1}{{n_{.1}}^{\alpha}} = E\,\frac{1}{{n_{.2}}^{\alpha}}\ , \quad (\alpha = 1,\,2,\,3,\,4)\ , \tag{68}$$

where $\Upsilon_{i,1}$ and $\Upsilon_{i,2}$ are the same as (28) and (35), respectively, with λ replaced by λ_i (these approximations can be seen in Equations (69), and (70)), and $\Upsilon_1, \ldots, \Upsilon_4$ are defined in (28), (35), (37) and (39) respectively; in this case we replace λ with $\sum_{i=1}^{N} \lambda_i$ (see Equations (71 – 74)).

As above, denote $\Lambda = \sum_{i=1}^{N} \lambda_i$. The approximations for the first four negative moments that are used in Section 6 are as follows:

$$\Upsilon_{i,1} = \frac{1}{\lambda_i} + \frac{1}{\lambda_i^2} + \frac{2}{\lambda_i^3} + \frac{6}{\lambda_i^4} \; ; \tag{69}$$

$$\Upsilon_{i,2} = \frac{1}{\lambda_i^2} + \frac{3}{\lambda_i^3} + \frac{11}{\lambda_i^4} + \frac{50}{\lambda_i^5} + \frac{274}{\lambda_i^6} + \frac{1\,764}{\lambda_i^7} + \frac{13\,068}{\lambda_i^8} \; ; \tag{70}$$

$$\Upsilon_1 = \frac{1}{\Lambda} + \frac{1}{\Lambda^2} + \frac{2}{\Lambda^3} + \frac{6}{\Lambda^4} \; ; \tag{71}$$

$$\Upsilon_2 = \frac{1}{\Lambda^2} + \frac{3}{\Lambda^3} + \frac{11}{\Lambda^4} + \frac{50}{\Lambda^5} + \frac{274}{\Lambda^6} + \frac{1\,764}{\Lambda^7} + \frac{13\,068}{\Lambda^8} \; ; \tag{72}$$

$$\Upsilon_3 = \sum_{u=3}^{12} \frac{s(u,3)}{\lambda^u} = \frac{1}{\Lambda^3} + \ldots + \frac{120\,543\,840}{\Lambda^{12}} \; ; \tag{73}$$

$$\Upsilon_4 = \sum_{u=4}^{16} \frac{s(u,4)}{\lambda^u} = \frac{1}{\Lambda^4} + \ldots + \frac{5\,056\,995\,703\,824}{\Lambda^{16}} \; . \tag{74}$$

In addition, similar to Section 5, since N is large, through using the asymptotic independence of n_{i1} and $n_{.1}$ we can state (for $k = 1, 2, 3, \ldots$) that

$$E\left(\frac{n_{i1}}{n_{.1}}\right)^k \simeq E\, n_{i1}^k\, E\frac{1}{n_{.1}^k} \;\text{ and }\; E\left(\frac{n_{i2}}{n_{.2}}\right)^k \simeq E\, n_{i2}^k\, E\frac{1}{n_{.2}^k} \; . \tag{75}$$

6.1 $\overline{MSE}(\Delta_I)$

Scenario I: Independent n_{i1} and n_{i2}

By definition (see (9)),

$$\begin{aligned} \overline{MSE}(\Delta_I) &= \sigma^2\left(\frac{1}{n_{.2}} + \frac{1}{n_{.1}}\right) + \sigma_\mu^2 \sum_{i=1}^{N}\left(\frac{n_{i2}}{n_{.2}} - \frac{n_{i1}}{n_{.1}}\right)^2 + \sigma_\tau^2 \sum_{i=1}^{N}\left(\frac{n_{i2}}{n_{.2}} + \frac{n_{i1}}{n_{.1}} - \frac{2}{N}\right)^2 \\ &= \sigma^2 \nu + \sigma_\mu^2 \sum_{i=1}^{N} \rho_i + \sigma_\tau^2 \sum_{i=1}^{N} \phi_i \; , \end{aligned}$$

where

$$\nu = \left(\frac{1}{n_{.2}} + \frac{1}{n_{.1}}\right) \; ; \quad \rho_i = \left(\frac{n_{i2}}{n_{.2}} - \frac{n_{i1}}{n_{.1}}\right)^2 \; ; \quad \phi_i = \left(\frac{n_{i2}}{n_{.2}} + \frac{n_{i1}}{n_{.1}} - \frac{2}{N}\right)^2 \; .$$

Using (66), (68) and (75), we obtain

$$E\,\nu = E\left(\frac{1}{n_{.2}} + \frac{1}{n_{.1}}\right) \simeq 2\Upsilon_1 \; ;$$

$$E\,\rho_i = E\left(\frac{n_{i2}^2}{n_{.2}^2}-\frac{2n_{i1}n_{i2}}{n_{.1}n_{.2}}+\frac{n_{i1}^2}{n_{.1}^2}\right)\simeq 2\left(\lambda_i+\lambda_i^2\right)\Upsilon_2-2\lambda_i^2\left(\Upsilon_1\right)^2 \;;$$

$$\begin{aligned} E\,\phi_i &= E\left(\frac{n_{i2}^2}{n_{.2}^2}+\frac{n_{i1}^2}{n_{.1}^2}+\frac{4}{N^2}+\frac{2n_{i2}n_{i1}}{n_{.2}n_{.1}}-\frac{4n_{i2}}{Nn_{.2}}-\frac{4n_{i1}}{Nn_{.1}}\right) \\ &\simeq 2\left(\lambda_i+\lambda_i^2\right)\Upsilon_2+\frac{4}{N^2}+2\lambda_i^2\Upsilon_1^2-\frac{8\lambda_i\Upsilon_1}{N} \;. \end{aligned}$$

Thus,

$$\begin{aligned} E\,\overline{MSE}(\Delta_I) &= \sigma^2 E\,\nu+\sigma_\mu^2\sum_{i=1}^N E\,\rho_i+\sigma_\tau^2\sum_{i=1}^N E\,\phi_i \\ &\simeq 2\sigma^2\Upsilon_1+\sigma_\mu^2\sum_{i=1}^N\left(2\left(\lambda_i+\lambda_i^2\right)\Upsilon_2-2\lambda_i^2\left(\Upsilon_1\right)^2\right) \\ &\quad+\sigma_\tau^2\sum_{i=1}^N\left(2\left(\lambda_i+\lambda_i^2\right)\Upsilon_2+\frac{4}{N^2}+2\lambda_i^2\Upsilon_1^2-\frac{8\lambda_i\Upsilon_1}{N}\right) \;, \end{aligned} \tag{76}$$

which can be evaluated by using the approximations in (71) and (72).

The second moment can be approximated as follows

$$\begin{aligned} E\left[\overline{MSE}(\Delta_I)\right]^2 &= E\left[\sigma^2\,\nu+\sigma_\mu^2\sum_{i=1}^N \rho_i+\sigma_\tau^2\sum_{i=1}^N\phi_i\right]^2 \\ &= \sigma^4 E\,\nu^2+\sigma_\mu^4\sum_{i,j}^N E\,\rho_i\rho_j+\sigma_\tau^4\sum_{i,j}^N E\,\phi_i\phi_j+2\sigma^2\sigma_\mu^2\sum_{i=1}^N E\,\nu\rho_i+2\sigma^2\sigma_\tau^2\sum_{i=1}^N E\,\nu\phi_i \\ &\quad+2\sigma_\mu^2\sigma_\tau^2\sum_{i,j}^N E\,\rho_i\phi_i \\ &\simeq \sigma^4 E\,\nu^2+\sigma_\mu^4\left[\sum_{i=1}^N E\,\rho_i^2+\sum_{i\neq j}^N E\,\rho_i\rho_j\right]+\sigma_\tau^4\left[\sum_{i=1}^N E\,\phi_i^2+\sum_{i\neq j}^N E\,\phi_i\phi_j\right]+2\sigma^2\sigma_\mu^2\sum_{i=1}^N E\,\nu\rho_i \\ &\quad+2\sigma^2\sigma_\tau^2\sum_{i=1}^N E\,\nu\phi_i+2\sigma_\mu^2\sigma_\tau^2\left[\sum_{i=1}^N E\,\rho_i\phi_i+\sum_{i\neq j}^N E\,\rho_i E\,\phi_j\right] \\ &= \sigma^4 E\,\nu^2+\sigma_\mu^4\left[\sum_{i=1}^N E\,\rho_i^2+\left(\sum_{i=1}^N E\,\rho_i\right)^2-\sum_{i=1}^N\left(E\,\rho_i\right)^2\right] \\ &\quad+\sigma_\tau^4\left[\sum_{i=1}^N E\,\phi_i^2+\left(\sum_{i=1}^N E\,\phi_i\right)^2-\sum_{i=1}^N\left(E\,\phi_i\right)^2\right]+2\sigma^2\sigma_\mu^2\sum_{i=1}^N E\,\nu\rho_i \\ &\quad+2\sigma^2\sigma_\tau^2\sum_{i=1}^N E\,\nu\phi_i+2\sigma_\mu^2\sigma_\tau^2\left[\sum_{i=1}^N E\,\rho_i\phi_i+\sum_{i=1}^N E\,\rho_i\sum_{j=1}^N E\,\phi_j-\sum_{i=1}^N E\,\rho_i E\,\phi_i\right] \end{aligned} \tag{77}$$

Using (66), (68) and (75) it can be shown that

$$E\,\nu^2 = E\left(\frac{1}{n_{.2}^2}+2\frac{1}{n_{.1}}\frac{1}{n_{.2}}+\frac{1}{n_{.1}^2}\right)\simeq 2\left(\Upsilon_2+\left(\Upsilon_1\right)^2\right) \;;$$

$$
\begin{aligned}
E\rho_i^2 &= E\left(\frac{n_{i2}^4}{n_{.2}^4}-\frac{4n_{i2}^3 n_{i1}}{n_{.2}^3 n_{.1}}+\frac{6n_{i2}^2 n_{i1}^2}{n_{.2}^2 n_{.1}^2}-\frac{4n_{i2}n_{i1}^3}{n_{.2}n_{.1}^3}+\frac{n_{i1}^4}{n_{.1}^4}\right)\\
&\simeq 2(\lambda_i+7\lambda_i^2+6\lambda_i^3+\lambda_i^4)\Upsilon_4-8(\lambda_i+3\lambda_i^2+\lambda_i^3)\lambda_i\Upsilon_3\Upsilon_1+6(\lambda_i+\lambda_i^2)^2\Upsilon_2^2\ ;\\
E\,\phi_i^2 &= E\left(\frac{n_{i2}^4}{n_{.2}^4}+\frac{n_{i1}^4}{n_{.1}^4}+\frac{16}{N^4}+\frac{4n_{i2}^3 n_{i1}}{n_{.2}^3 n_{.1}}+\frac{6n_{i2}^2 n_{i1}^2}{n_{.2}^2 n_{.1}^2}+\frac{4n_{i2}n_{i1}^3}{n_{.2}n_{.1}^3}-\frac{8n_{i2}^3}{Nn_{.2}^3}+\frac{24n_{i2}^2}{N^2 n_{.2}^2}-\frac{32n_{i2}}{N^3 n_{.2}}\right.\\
&\quad\left.-\frac{8n_{.1}^3}{Nn_{.1}^3}+\frac{24n_{i1}^2}{N^2 n_{.1}^2}-\frac{32n_{i1}}{N^3 n_{.1}}-\frac{24n_{i2}^2 n_{i1}}{Nn_{.2}^2 n_{.1}}-\frac{24n_{i2}n_{i1}^2}{Nn_{.2}n_{.1}^2}+\frac{48n_{i2}n_{i1}}{N^2 n_{.2}n_{.1}}\right)\\
&\simeq 2\left(\lambda_i+7\lambda_i^2+6\lambda_i^3+\lambda_i^4\right)\Upsilon_4+\frac{16}{N^4}+\frac{48\left(\lambda_i+\lambda_i^2\right)\Upsilon_2}{N^2}-\frac{48\left(\lambda_i+\lambda_i^2\right)\lambda_i\Upsilon_2\Upsilon_1}{N}-\frac{64\lambda_i\Upsilon_1}{N^3}\\
&\quad+6\left(\lambda_i+\lambda_i^2\right)^2\Upsilon_2^2+\frac{48\lambda_i^2\Upsilon_1^2}{N^2}+8\left(\lambda_i+3\lambda_i^2+\lambda_i^3\right)\lambda_i\Upsilon_3\Upsilon_1-\frac{16\left(\lambda_i+3\lambda_i^2+\lambda_i^3\right)\Upsilon_3}{N}\ ;\\
E\,\nu\rho_i &= E\left(\frac{n_{i2}^2}{n_{.2}^3}-\frac{2n_{i2}n_{i2}}{n_{.2}^2 n_{.1}}+\frac{n_{i1}^2}{n_{i2}n_{i1}^2}+\frac{n_{i2}^2}{n_{.2}^2 n_{i1}}-\frac{2n_{i2}n_{i1}}{n_{.2}n_{.1}^2}+\frac{n_{i1}^2}{n_{.1}^3}\right)\\
&\simeq 2\left(\lambda_i+\lambda_i^2\right)\Upsilon_3-4\lambda_i^2\Upsilon_2\Upsilon_1+2\left(\lambda_i+\lambda_i^2\right)\Upsilon_2\Upsilon_1\ ;\\
E\,\nu\phi_i &= E\left(\frac{n_{i2}^2}{n_{.2}^3}+\frac{n_{i1}^2}{n_{.2}n_{.1}^2}+\frac{4}{N^2 n_{.2}}+\frac{2n_{i2}n_{i1}}{n_{.2}^2 n_{.1}}-\frac{4n_{i2}}{Nn_{.2}^2}-\frac{4n_{i1}}{Nn_{.2}n_{.1}}+\frac{n_{i2}^2}{n_{.2}^2 n_{.1}}+\frac{n_{i1}^2}{n_{.1}^3}\right.\\
&\quad\left.+\frac{4}{N^2 n_{.1}}+\frac{2n_{i2}n_{i1}}{n_{.2}n_{.1}^2}-\frac{4n_{i2}}{Nn_{.2}n_{.1}}-\frac{4n_{i1}}{Nn_{.1}^2}\right)\\
&\simeq 2\left(\lambda_i+\lambda_i^2\right)\left(\Upsilon_3+\Upsilon_2\Upsilon_1\right)+\frac{8\Upsilon_1}{N^2}+4\lambda_i^2\Upsilon_2\Upsilon_1-\frac{8\lambda_i\left(\Upsilon_1\right)^2}{N}-\frac{8\lambda_i\Upsilon_2}{N}\ ;\\
E\,\rho_i\phi_i &= E\left(\frac{n_{i2}^4}{n_{.2}^4}-\frac{2n_{i2}^2 n_{i1}^2}{n_{.2}^2 n_{.1}^2}-\frac{4n_{i2}^3}{Nn_{.2}^3}+\frac{4n_{i2}^2 n_{i1}}{Nn_{.2}^2 n_{.1}}+\frac{4n_{i2}n_{i1}^2}{Nn_{.2}n_{.1}^2}+\frac{n_{i1}^4}{n_{.1}^4}-\frac{4n_{i1}^3}{n_{.1}^3}\right.\\
&\quad\left.+\frac{4n_{i2}^2}{N^2 n_{.2}^2}-\frac{8n_{i2}n_{i1}}{N^2 n_{.2}n_{.1}}+\frac{4n_{i1}^2}{N^2 n_{.1}^2}\right)\\
&\simeq 2\left(\lambda_i+7\lambda_i^2+6\lambda_i^3+\lambda_i^4\right)\Upsilon_4-2\left(\lambda_i+\lambda_i^2\right)^2\Upsilon_2^2-\frac{8\left(\lambda_i+3\lambda_i^2+\lambda_i^3\right)\Upsilon_3}{N}\\
&\quad+\frac{8\left(\lambda_i+\lambda_i^2\right)\lambda_i\Upsilon_2\Upsilon_1}{N}+\frac{8\left(\lambda_i+\lambda_i^2\right)\Upsilon_2}{N^2}-\frac{8\lambda_i^2\Upsilon_1^2}{N^2}\ .
\end{aligned}
$$

Thus, our approximation for $E\left[\overline{MSE}\left(\Delta_I\right)\right]^2$ is obtained through substituting the above approximations into (77), and can be evaluated by using the approximations in (71) – (74).

The variance of $\overline{MSE}\left(\Delta_I\right)$ is then obtained through substituting (76) and (77) into

$$
Var\,\overline{MSE}\left(\Delta_I\right)=E\left[\overline{MSE}\left(\Delta_I\right)\right]^2-\left[E\,\overline{MSE}\left(\Delta_I\right)\right]^2 .
$$

Scenario II: Dependent recruitment, $n_{i1}=n_{i2}=n_i$

In Scenario II, the term associated with centre effect is now equal to zero. Hence, we have

$$\overline{MSE}(\Delta_I^*) \;=\; \sigma^2\nu^* + \sigma_\tau^2\sum_{i=1}^{N}\phi_i^* \;,$$

with

$$\nu^* = \frac{2}{n_.}\,, \quad \text{and} \quad \phi_i^* = 4\left(\frac{n_i}{n_.} - \frac{1}{N}\right)^2 .$$

Using (66), (68) and (75) we obtain

$$E\,\nu^* = E\,\frac{2}{n_.} \simeq 2\Upsilon_1\,;\; E\,\phi_i^* = 4E\left(\frac{n_i^2}{n_.^2} - \frac{2n_i}{Nn_.} + \frac{1}{N^2}\right) \simeq 4\left(\lambda_i + \lambda_i^2\right)\Upsilon_2 - \frac{8\lambda_i\Upsilon_1}{N} + \frac{4}{N^2}\,.$$

Thus,

$$\begin{aligned} E\,\overline{MSE}(\Delta_I^*) &= \sigma^2 E\,\nu^* + \sigma_\tau^2\sum_{i=1}^{N}E\,\phi_i^* \\ &\simeq 2\sigma^2\Upsilon_1 + \sigma_\tau^2\sum_{i=1}^{N}\left(4\left(\lambda_i+\lambda_i^2\right)\Upsilon_2 - \frac{8\lambda_i\Upsilon_1}{N} + \frac{4}{N^2}\right), \end{aligned} \tag{78}$$

which can be evaluated using Equations (71) and (72).

The second moment can be derived in a similar manner to that of Scenario I, the sole difference being that terms involving ρ_i are omitted. Thus, from (77) we obtain

$$\begin{aligned} E\,\left[\overline{MSE}(\Delta_I^*)\right]^2 &= \sigma^4 E\,\nu^{*\,2} + \sigma_\tau^4\left[\sum_{i=1}^{N}E\,\phi_i^{*\,2} + \left(\sum_{i=1}^{N}E\,\phi_i^*\right)^2 - \sum_{i=1}^{N}(E\,\phi_i^*)^2\right] \\ &\quad + 2\sigma^2\sigma_\tau^2\sum_{i=1}^{N}E\,\nu^*\phi_i^*\,. \end{aligned} \tag{79}$$

Using (66), (68) and (75), we obtain

$$\begin{aligned} E\,\nu^{*\,2} &\simeq E\,\frac{4}{n_.^2} = 4\Upsilon_2\,; \\ E\,\phi_i^{*\,2} &= 16E\left(\frac{n_i^4}{n_.^4} - \frac{4n_i^3}{Nn_.^3} + \frac{6n_i^2}{N^2n_.^2} - \frac{4n_i}{N^3n_.} + \frac{1}{N^4}\right) \\ &\simeq 16\left[(\lambda_i+7\lambda_i^2+6\lambda_i^3+\lambda_i^4)\Upsilon_4 - \frac{4(\lambda_i+3\lambda_i^2+\lambda_i^3)\Upsilon_3}{N} + \frac{6\left(\lambda_i+\lambda_i^2\right)\Upsilon_2}{N^2} - \frac{4\lambda_i\Upsilon_1}{N^3} + \frac{1}{N^4}\right]; \\ E\,\nu^*\phi_i^* &= 8E\left(\frac{n_i^2}{n_.^3} - \frac{2n_i}{Nn_.^2} + \frac{1}{N^2n_.}\right) \simeq 8\left[\left(\lambda_i + \lambda_i^2\right)\Upsilon_3 - \frac{2\lambda_i\Upsilon_2}{N} + \frac{\Upsilon_1}{N^2}\right]. \end{aligned}$$

By substituting these approximations into (79) and using the approximations in (71) – (74) we obtain our estimate of the second moment for $\overline{MSE}\,(\Delta_I^*)$. The variance is then obtained by substituting (78) and (79) into

$$Var\,\overline{MSE}\,(\Delta_I^*) = E\,\left[\overline{MSE}\,(\Delta_I^*)\right]^2 - \left[E\,\overline{MSE}\,(\Delta_I^*)\right]^2 .$$

6.2 $\overline{MSE}(\Delta_{II})$

Scenario I: Independent n_{i1} and n_{i2}

From (10) we have

$$\begin{aligned}\overline{MSE}(\Delta_{II}) &= \sigma^2 \sum_{i=1}^{N} W_i^2 \left(\frac{1}{n_{i2}} + \frac{1}{n_{i1}}\right) + 4\sigma_\tau^2 \sum_{i=1}^{N} \left(W_i - \frac{1}{N}\right)^2 \\ &= \sigma^2 \sum_{i=1}^{N} \eta_i + 4\sigma_\tau^2 \sum_{i=1}^{N} \vartheta_i\,.\end{aligned}$$

Using (43) and (44), we obtain

$$\begin{aligned}\eta_i &= W_i^2 \left(\frac{1}{n_{i2}} + \frac{1}{n_{i1}}\right) = \frac{\frac{n_{i1}n_{i2}}{n_{i1}+n_{i2}}}{\left(\sum_{i=1}^{N} \frac{n_{i1}n_{i2}}{n_{i1}+n_{i2}}\right)^2} = \frac{\omega_i}{\omega^2}\,; \\ \vartheta_i &= \left(W_i - \frac{1}{N}\right)^2 = \frac{\omega_i^2}{\omega^2} - \frac{2\,\omega_i}{N\omega} + \frac{1}{N^2}\,.\end{aligned}$$

Equation (52) gives

$$E\,\eta_i \simeq \frac{E\,\omega_i}{E\,\omega^2}\,, \quad E\,\vartheta_i \simeq \frac{E\,\omega_i^2}{E\,\omega^2} - \frac{2E\,\omega_i}{NE\,\omega} + \frac{1}{N^2}\,.$$

Thus,

$$\begin{aligned}E\,\overline{MSE}(\Delta_{II}) &= \sigma^2 \sum_{i=1}^{N} E\,\eta_i + 4\sigma_\tau^2 \sum_{i=1}^{N} E\,\vartheta_i \\ &\simeq \sigma^2 \sum_{i=1}^{N} \frac{E\,\omega_i}{E\,\omega^2} + 4\sigma_\tau^2 \sum_{i=1}^{N} \left(\frac{E\,\omega_i^2}{E\,\omega^2} - \frac{2E\,\omega_i}{NE\,\omega} + \frac{1}{N^2}\right)\,, \qquad (80)\end{aligned}$$

which can be evaluated by substituting in the approximations from (45), (46), (49) and (53).

The second moment can be approximated as follows:

$$\begin{aligned}E\left[\overline{MSE}(\Delta_{II})\right]^2 &= E\left[\sigma^2 \sum_{i=1}^{N} \eta_i + 4\sigma_\tau^2 \sum_{i=1}^{N} \vartheta_i\right]^2 \\ &= \sigma^4 \sum_{i,j}^{N} E\,\eta_i\eta_j + 16\sigma_\tau^4 \sum_{i,j}^{N} E\,\vartheta_i\vartheta_j + 8\sigma^2\sigma_\tau^2 \sum_{i,j}^{N} E\,\eta_i\vartheta_i \\ &= \sigma^4 \left[\sum_{i=1}^{N} E\,\eta_i^2 + \sum_{i\neq j}^{N} E\,\eta_i\eta_j\right] + 16\sigma_\tau^4 \left[\sum_{i=1}^{N} E\,\vartheta_i^2 + \sum_{i\neq j}^{N} E\,\vartheta_i\vartheta_j\right] + 8\sigma^2\sigma_\tau^2 \left[\sum_{i=1}^{N} E\,\eta_i\vartheta_i + \sum_{i\neq j}^{N} E\,\eta_i\vartheta_j\right] \\ &\simeq \sigma^4 \left[\sum_{i=1}^{N} E\,\eta_i^2 + \left(\sum_{i=1}^{N} E\,\eta_i\right)^2 - \sum_i (E\,\eta_i)^2\right] + 16\sigma_\tau^4 \left[\sum_{i=1}^{N} E\,\vartheta_i^2 + \left(\sum_{i=1}^{N} E\,\vartheta_i\right)^2 - \sum_i (E\,\vartheta_i)^2\right] \\ &\quad + 8\sigma^2\sigma_\tau^2 \left[\sum_{i=1}^{N} E\,\eta_i\vartheta_i + \sum_{i=1}^{N} E\,\eta_i \sum_{j=1}^{N} E\,\vartheta_j - \sum_i E\,\eta_i E\,\vartheta_i\right]\,. \qquad (81)\end{aligned}$$

Equation (52) gives

$$
\begin{aligned}
E\,\eta_i^2 &= E\left(\frac{\omega_i}{\omega^2}\right)^2 \simeq \frac{E\,\omega_i^2}{E\,\omega^4}\,;\\
E\,\vartheta_i^2 &= E\left(\frac{\omega_i}{\omega}-\frac{1}{N}\right)^4 \simeq \frac{E\,\omega_i^4}{E\,\omega^4}+\frac{6E\,\omega_i^2}{N^2E\,\omega^2}+\frac{1}{N^4}-\frac{4E\,\omega_i^3}{NE\,\omega^3}-\frac{4E\,\omega_i}{N^3E\,\omega}\,;\\
E\,\eta_i\vartheta_i &= E\left[\frac{\omega_i}{\omega^2}\left(\frac{\omega_i^2}{\omega^2}-\frac{2\omega_i}{N\omega}+\frac{1}{N^2}\right)\right] \simeq \frac{E\,\omega_i^3}{E\,\omega^4}-\frac{2E\,\omega_i^2}{NE\,\omega^3}+\frac{E\omega_i}{N^2E\,\omega^2}\,.
\end{aligned}
$$

The above expectations can be approximated using (45), (46), (47), (48), (49), (53), (54) and (55). We then obtain $E\left[\overline{MSE}\,(\Delta_{II})\right]^2$ by substituting all the approximations into (81).

The variance is then obtained by substituting (80) and (81) into

$$
Var\,\overline{MSE}\,(\Delta_{II}) = E\,\left[\overline{MSE}\,(\Delta_{II})\right]^2 - \left[E\,\overline{MSE}\,(\Delta_{II})\right]^2\,.
$$

Scenario II: Dependent recruitment, $n_{i1} = n_{i2} = n_i$

Approximations for the first two moments of $\overline{MSE}\,(\Delta_{II})$ under Scenario II are generated in an almost identical manner to that of Scenario I. The only difference being that the approximations $E\,\omega_i^k$ and $E\,\omega^k$ $(k = 1, 2, 3, 4)$ are replaced by their corresponding approximations for Scenario II, namely, $E\,\omega_i^{*\,k}$ and $E\,\omega^{*\,k}$ (defined in Section 5).

Thus,

$$
\begin{aligned}
\overline{MSE}(\Delta_{II}^*) &= \sigma^2\sum_{i=1}^N W_i^{*\,2}\left(\frac{2}{n_i}\right)+4\sigma_\tau^2\sum_{i=1}^N\left(W_i^*-\frac{1}{N}\right)\\
&= \sigma^2\sum_{i=1}^N \eta_i^* + 4\sigma_\tau^2\sum_{i=1}^N \vartheta_i^*\,.
\end{aligned}
$$

Using (56) and (57), we obtain

$$
\begin{aligned}
\eta_i^* &= W_i^{*\,2}\left(\frac{2}{n_i}\right) = \frac{\frac{n_i}{2}}{\left(\sum_{i=1}^N\frac{n_i}{2}\right)^2} = \frac{\omega_i^*}{\omega^{*\,2}}\,;\\
\vartheta_i^* &= \left(W_i^*-\frac{1}{N}\right)^2 = \frac{\omega_i^{*\,2}}{\omega^{*\,2}}-\frac{2\omega_i^*}{N\omega^*}+\frac{1}{N^2}\,.
\end{aligned}
$$

By assuming (52) also applies for the dependent case, we have

$$
E\,\eta_i^* \simeq \frac{E\,\omega_i^*}{E\,\omega^{*\,2}}\,;\quad E\,\vartheta_i^* \simeq \frac{E\,\omega_i^{*\,2}}{E\,\omega^{*\,2}}-\frac{2E\,\omega_i^*}{NE\,\omega^*}+\frac{1}{N^2}\,.
$$

Thus,

$$
\begin{aligned}
E\,\overline{MSE}(\Delta_{II}^*) &= \sigma^2\sum_{i=1}^N E\,\eta_i^* + 4\sigma_\tau^2\sum_{i=1}^N E\,\vartheta_i\\
&\simeq \sigma^2\sum_{i=1}^N\frac{E\,\omega_i^*}{E\,\omega^{*\,2}}+4\sigma_\tau^2\sum_{i=1}^N\left(\frac{E\,\omega_i^{*\,2}}{E\,\omega^{*\,2}}-\frac{2E\,\omega_i^*}{NE\,\omega^*}+\frac{1}{N^2}\right)\,. \qquad (82)
\end{aligned}
$$

This can be evaluated using the approximations from (58), (59), (62) and (63).

The second moment of $\overline{MSE}(\Delta^*_{II})$ can be derived in a similar manner to the method used in (81)

$$E\left[\overline{MSE}(\Delta^*_{II})\right]^2 \simeq \sigma^4\left[\sum_{i=1}^N E\,\eta_i^{*\,2} + \left(\sum_{i=1}^N E\,\eta_i^*\right)^2 - \sum_i (E\,\eta_i^*)^2\right] + 16\sigma_\tau^4\left[\sum_{i=1}^N E\,\vartheta_i^{*\,2}\right.$$
$$\left. + \left(\sum_{i=1}^N E\,\vartheta_i^*\right)^2 - \sum_i (E\,\vartheta_i^*)^2\right] + 8\sigma^2\sigma_\tau^2\left[\sum_{i=1}^N E\,\eta_i^*\vartheta_i^* + \sum_{i=1}^N E\,\eta_i^* \sum_{j=1}^N E\,\vartheta_j^* - \sum_i E\,\eta_i^* E\,\vartheta_i^*\right], \qquad (83)$$

where using (52) we have

$$E\,\eta_i^{*\,2} = E\left(\frac{\omega_i^*}{\omega^{*\,2}}\right)^2 \simeq \frac{E\,\omega_i^{*\,2}}{E\,\omega^{*\,4}}\,;$$
$$E\,\vartheta_i^{*\,2} = E\left(\frac{\omega_i^*}{\omega^*} - \frac{1}{N}\right)^4 \simeq \frac{E\,\omega_i^{*\,4}}{E\,\omega^{*\,4}} + \frac{6E\,\omega_i^{*\,2}}{N^2 E\,\omega^{*\,2}} + \frac{1}{N^4} - \frac{4E\,\omega_i^{*\,3}}{NE\,\omega^{*\,3}} - \frac{4E\,\omega_i^*}{N^3 E\,\omega^*}\,;$$
$$E\,\eta_i^*\vartheta_i^* = E\left[\frac{\omega_i^*}{\omega^{*\,2}}\left(\frac{\omega_i^{*\,2}}{\omega^{*\,2}} - \frac{2\omega_i^*}{N\omega^*} + \frac{1}{N^2}\right)\right] \simeq \frac{E\,\omega_i^{*\,3}}{E\,\omega^{*\,4}} - \frac{2E\,\omega_i^{*\,2}}{NE\,\omega^{*\,3}} + \frac{E\omega_i^*}{N^2 E\,\omega^{*\,2}}\,.$$

These expectations can be evaluated using the approximations from (58) – (65). We then substitute these approximations into (83) to approximate $E\left[\overline{MSE}\,(\Delta^*_{II})\right]^2$.

An approximation of the variance is obtained through the substitution of the approximations (82) and (83) into

$$Var\,\overline{MSE}\,(\Delta^*_{II}) = E\left[\overline{MSE}\,(\Delta^*_{II})\right]^2 - \left[E\,\overline{MSE}\,(\Delta^*_{II})\right]^2\,.$$

6.3 $\overline{MSE}(\Delta_{III})$

Scenario I: Independent n_{i1} and n_{i2}

Let $\overline{MSE}(\Delta_{III}) = \frac{1}{N^2}\sum_{i=1}^N \zeta_i$, where

$$\zeta_i = \begin{cases} \sigma^2\left(\frac{1}{n_{i1}} + \frac{1}{n_{i2}}\right) & \text{if } n_{i1} > 0, n_{i2} > 0\,, \\ 4\left(\sigma_\tau^2 + 1\right) & \text{if } n_{i1} = 0 \text{ or } n_{i2} = 0\,. \end{cases}$$

The mean of the $\overline{MSE}(\Delta_{III})$ is

$$E\,\overline{MSE}(\Delta_{III}) = \frac{1}{N^2}\sum_{i=1}^N E(\zeta_i)\,.$$

It can be shown that

$$E\left(\zeta_i\right) = (1-p_{0i})^2\sigma^2\left(E\,\frac{1}{n_{i1}} + E\,\frac{1}{n_{i2}}\right) + 4\left(\sigma_\tau^2+1\right)\left(2p_{0i} - p_{0i}^2\right)\,,$$

with $p_{0i} = e^{-\lambda_i}$ representing the probability of there being zero patients on either treatment arm. As we are considering the case where $\lambda_i \geq 10$, p_{0i} is negligible and will consequently be omitted from the subsequent approximations of the first two moments of $\overline{MSE}(\Delta_{III})$ for both Scenarios I and II.

Thus,

$$E\,\overline{MSE}(\Delta_{III}) \quad \simeq \quad \frac{2\sigma^2}{N^2}\sum_{i=1}^{N}\Upsilon_{i,1}\,, \tag{84}$$

where $\Upsilon_{i,1}$ is the approximation for the first negative moment of n_{i1} (and n_{i2}), see (67).

Similarly, the second moment of ζ_i is found as follows:

$$E\left(\zeta_i^2\right) = \sigma^4\left(E\,\frac{1}{n_{i1}^2} + E\,\frac{1}{n_{i2}^2} + 2E\,\frac{1}{n_{i1}}E\,\frac{1}{n_{i2}}\right) \simeq 2\sigma^4\left(\Upsilon_{i,2} + \Upsilon_{i,1}^2\right)\;,$$

thus,

$$E\,\left[\overline{MSE}(\Delta_{III})\right]^2 \quad \simeq \quad \frac{2\sigma^4}{N^4}\left(\Upsilon_{i,2} + \Upsilon_{i,1}^2\right)\,. \tag{85}$$

The variance of ζ_i is

$$\begin{aligned}
Var(\zeta_i) &= E(\zeta_i^2) - (E(\zeta_i))^2 \\
&= \sigma^4\left(E\,\frac{1}{n_{i1}^2} + E\,\frac{1}{n_{i2}^2} + 2E\,\frac{1}{n_{i1}}E\,\frac{1}{n_{i2}}\right) - \left(\sigma^2\left(E\,\frac{1}{n_{i1}} + E\,\frac{1}{n_{i2}}\right)\right)^2 \\
&= Var\frac{1}{n_{i1}} + Var\frac{1}{n_{i2}}\;,
\end{aligned}$$

through using the fact that $Var\,\frac{1}{n_{i1}} = Var\,\frac{1}{n_{i2}} \simeq \Upsilon_{i,2} - (\Upsilon_{i,1})^2$, we obtain

$$Var(\overline{MSE}(\Delta_{III})) \simeq \frac{2\sigma^4}{N^4}\sum_{i=1}^{N}\left(\Upsilon_{i,2} - (\Upsilon_{i,1})^2\right)\;. \tag{86}$$

Scenario II: Dependent recruitment, $n_{i1} = n_{i2} = n_i$

Let $\overline{MSE}(\Delta_{III}) = \frac{1}{N^2}\sum_{i=1}^{N}\zeta_i^*$, where

$$\zeta_i^* = \frac{2\sigma^2}{n_i}\,.$$

The mean of the $\overline{MSE}(\Delta_{III}^*)$ is

$$E\,\overline{MSE}(\Delta_{III}^*) \quad = \quad \frac{1}{N^2}\sum_{i=1}^{N}E(\zeta_i^*)\,,$$

we can use the approximation

$$E\,\zeta_i^* \simeq 2\sigma^2 \Upsilon_{i,1}\,, \tag{87}$$

thus,

$$E\,\overline{MSE}(\Delta_{III}^*) \;\; \simeq \;\; \frac{2\sigma^2}{N^2}\sum_{i=1}^{N}\Upsilon_{i,1}\,.$$

The second moment of ζ_i^* can be approximated as follows:

$$E\,\zeta_i^{*\,2} = E\left(\frac{2\sigma^2}{n_i}\right)^2 \simeq 4\sigma^4\Upsilon_{i,2}\,, \tag{88}$$

thus, we have

$$E\,\left[\overline{MSE}(\Delta_{III}^*)\right]^2 \;\; \simeq \;\; \frac{4\sigma^4}{N^4}\sum_{i=1}^{N}\Upsilon_{i,2}\,.$$

Equations (87) and (88) give the variance of ζ_i^* as

$$Var(\zeta_i^*) \;\; = \;\; E(\zeta_i^{*\,2}) - (E(\zeta_i^*))^2 \simeq 4\sigma^4\left(\Upsilon_{i,2} - (\Upsilon_{i,1})^2\right)\,.$$

Hence,

$$Var\;\overline{MSE}(\Delta_{III}^*) \simeq \frac{4\sigma^4}{N^4}\sum_{i=1}^{N}\left(\Upsilon_{i,2} - (\Upsilon_{i,1})^2\right)\,. \tag{89}$$

It is found through comparing (86) and (89) that the variance of $\overline{MSE}(\Delta_{III})$ is exactly twice as large for Scenario II than Scenario I, if we ignore $p_{0,\,i}$ $(i = 1, 2)$; the probability of there being zero patients on either of the treatment arms. This result coincides with the results of the simulation study shown in Table III, that the standard deviation of $\overline{MSE}_{(}\Delta_{III})$ is approximately $\sqrt{2}$ times larger in Scenario II compared with Scenario I.

7. ACCURACY OF THE APPROXIMATIONS

The accuracy of the approximations for the first two moments of $\overline{MSE}(\Delta_I) - \overline{MSE}(\Delta_{III})$ under Scenario I and II are assessed in this section. This is achieved through the comparison of our theoretical results with those obtained from a simulation study performed in S-Plus (see Fedorov et al. (18)) for the two enrollment cases outlined in Section 2. For ease of interpretation the results (for both theoretical and simulated) that are summarised in Table III are normalised, that is, the $\overline{MSE}$ values are multiplied by the mean total number of patients (in our case $E(n_{.1}) + E(n_{.2}) = 2\sum_{i=1}^{N}\lambda_i = 2\,000$).

We discover some interesting results by studying Table III. In general the theoretical approximations appear to be reasonably accurate, with the value for the both $E\,\overline{MSE}$ and

Statistic			CASE I		CASE II	
			$E\,\overline{MSE}$	$E\left(\overline{MSE}\right)^2$	$E\,\overline{MSE}$	$E\left(\overline{MSE}\right)^2$
$\overline{MSE}(\Delta_I)$	Scen. I	Simul.	4.4536	19.8672	4.4900	20.1727
		Approx.	4.5559	20.8002	4.5105	20.3599
	Scen. II	Simul.	4.4542	19.8892	4.4903	20.1881
		Approx.	4.5559	20.8450	4.5105	20.3749
$\overline{MSE}(\Delta_{II})$	Scen. I	Simul.	4.2510	18.0921	4.5054	20.3137
		Approx.	4.2475	18.7157	4.5094	20.3518
	Scen. II	Simul.	4.4542	19.9052	4.4903	20.1881
		Approx.	4.4456	19.8132	4.4905	20.1647
$\overline{MSE}(\Delta_{III})$	Scen. I	Simul.	4.0404	16.3337	4.5206	20.4624
		Approx.	4.0408	16.3368	4.5040	20.3060
	Scen. II	Simul.	4.0404	16.3415	4.5169	20.4461
		Approx.	4.0408	16.3453	4.5040	20.3261

Table III: Summary statistics comparing simulated and approximated values for the first two moments of $\overline{MSE}(\Delta_I)$ – $\overline{MSE}(\Delta_{III})$ for Scenarios I and II, in both Cases I and II.

$E\left(\overline{MSE}\right)^2$ corresponding closely with the simulated values in the majority of cases. The most marked difference in the table occurs between the approximation for the second moment of $\overline{MSE}(\Delta_I)$ and $\overline{MSE}(\Delta_{II})$ in Case I. The reason for this, for both estimators, is perhaps due to N being small. This causes the assumption of asymptotic independence of n_{i1} and $n_{.1}$ (also that of n_{i2} and $n_{.2}$) made in (75), that we use in our approximations for $E\left(\overline{MSE}(\Delta_I)\right)^2$, to be inaccurate. Similarly, the assumption of asymptotic independence of ω_i and ω made in (52), that is used in our subsequent approximations for $E\left(\overline{MSE}(\Delta_{II})\right)^2$, is also inaccurate. Consequently, the approximation for $E\left(\overline{MSE}\right)^2$ becomes inflated for both of these estimators in Case I.

By looking at the table it is clearly evident that the approximations for the first two moments of $\overline{MSE}(\Delta_{III})$ are very accurate in both Cases.

Thus, we can conclude that the approximations prove to be adequate, as inaccuracies can be explained by either a lack of patients, or alternatively a lack of centres in the trial. Thus, it would appear appropriate only to use the approximations when the multi-centre trial has adequate patient numbers being recruited to each centre, say $\lambda \geq 20$, and also a sufficient number of centres to assume asymptotic independence, for example $N \geq 100$.

APPENDIX

Approximations for mean of ω^3 and ω^4

As stated in Section 6 approximations for $E\,\omega^3$ and $E\,\omega^4$ can be obtained by applying the same technique as that used in finding $E\,\omega^2$ (see Equation (53)). For $E\,\omega^3$ we use the approximations of Equations (45), (46) and (47).

Thus

$$\begin{aligned}
\omega^3 &= \sum_i^N \sum_j^N \sum_k^N \omega_i \omega_j \omega_k \,. \\
E\,\omega^3 &= \sum_{i,\,j,\,k}^N E(\omega_i\omega_j\omega_k) = \sum_{i\neq j\neq k}^N E\,\omega_i\omega_j\omega_k + 3\sum_{j\neq i}^N E\,\omega_i^2\omega_j + \sum_{i=1}^N E\,\omega_i^3 \\
&\simeq \sum_{i\neq j\neq k}^N E\,\omega_i E\,\omega_j E\,\omega_k + 3\sum_{j\neq i}^N E\,\omega_i^2 E\,\omega_j + \sum_{i=1}^N E\,\omega_i^3 \\
&= \sum_{i=1}^N \sum_{j=1}^N \sum_{k=1}^N E\,\omega_i\, E\,\omega_j\, E\,\omega_k - 3\sum_{j\neq i}^N (E\,\omega_i)^2\; E\,\omega_j - \sum_{i=1}^N (E\,\omega_i)^3 + 3\sum_{j\neq i}^N E\,\omega_i^2\, E\,\omega_j + \sum_{i=1}^N E\,\omega_i^3 \\
&\simeq \left[\sum_{i=1}^N E\,\omega_i\right]^3 - 3\sum_{i=1}^N \sum_{j=1}^N \left[(E\,\omega_i)^2 - E\,\omega_i^2\right] E\,\omega_j + 3\sum_{i=1}^N \left[(E\,\omega_i)^2 - E\,\omega_i^2\right] E\,\omega_i \\
&\quad - \sum_{i=1}^N (E\,\omega_i)^3 + \sum_{i=1}^N E\,\omega_i^3 \\
&\simeq \left[\sum_{i=1}^N \left(\frac{\lambda_i}{2} - \frac{1}{4}\right)\right]^3 + 3\sum_{i=1}^N \left(\frac{\lambda_i}{8} + \frac{1}{8}\right) \sum_{j=1}^N \left(\frac{\lambda_j}{2} - \frac{1}{4}\right) + \sum_{i=1}^N \left(\frac{\lambda_i}{32} - \frac{7}{32}\right) \\
&\simeq \frac{1}{8}\left[\sum_{i=1}^N \left(\lambda_i - \frac{1}{2}\right)\right]^3 + \frac{3}{16}\sum_{i=1}^N (\lambda_i + 1) \sum_{j=1}^N \left(\lambda_j - \frac{1}{2}\right) + \frac{1}{32}\sum_{i=1}^N (\lambda_i - 7) \,.
\end{aligned}$$

To derive an approximation for $E\,\omega^4$ we use the approximations of (45), (46), (47) and (48). Thus,

$$\begin{aligned}
\omega^4 &= \sum_i^N \sum_j^N \sum_k^N \sum_l^N \omega_i\omega_j\omega_k\omega_l \,. \\
E\,\omega^4 &= \sum_{i,j,k,l}^N E(\omega_i\omega_j\omega_k\omega_l) = \sum_{i\neq j\neq k\neq l}^N E\,\omega_i\omega_j\omega_k\omega_l + 4\sum_{j\neq i}^N E\,\omega_i^3\omega_j + 3\sum_{j\neq i}^N E\omega_i^2\,\omega_j^2 + \sum_{i=1}^N E\,\omega_i^4 \\
&\simeq \sum_{i\neq j\neq k\neq l}^N E\,\omega_i E\,\omega_j E\,\omega_k E\,\omega_l + 4\sum_{j\neq i}^N E\,\omega_i^3 E\,\omega_j + 3\sum_{j\neq i}^N E\omega_i^2\, E\,\omega_j^2 + \sum_{i=1}^N E\,\omega_i^4 \\
&= \sum_{i,j,k,l}^N E\,\omega_i E\,\omega_j E\,\omega_k E\,\omega_l - 4\sum_{j\neq i}^N (E\,\omega_i)^3 E\,\omega_j - 3\sum_{j\neq i}^N (E\omega_i)^2\,(E\,\omega_j)^2 - \sum_{i=1}^N (E\,\omega_i)^4
\end{aligned}$$

$$+4\sum_{j\neq i}^{N} E\,\omega_i^3 E\,\omega_j + 3\sum_{j\neq i}^{N} E\omega_i^2\, E\,\omega_j^2 + \sum_{i=1}^{N} E\,\omega_i^4$$

$$= \left[\sum_{i=1}^{N} E\,\omega_i\right]^4 - 4\sum_{i=1}^{N}\left[(E\,\omega_i)^3 - E\,\omega_i^3\right]\sum_{j=1}^{N} E\,\omega_j + 4\sum_{i=1}^{N}\left[(E\,\omega_i)^3 - E\,\omega_i^3\right] E\,\omega_i$$

$$-3\left[\sum_{i=1}^{N}(E\,\omega_i)^2\right]^2 + 3\sum_{i=1}^{N}(E\,\omega_i)^4 + 3\left[\sum_{i=1}^{N} E\,\omega_i^2\right]^2 - 3\sum_{i=1}^{N}\left(E\,\omega_i^2\right)^2 - \sum_{i=1}^{N}(E\,\omega_i)^4 + \sum_{i=1}^{N} E\,\omega_i^4$$

$$\simeq \left[\sum_{i=1}^{N}\left(\frac{\lambda_i}{2} - \frac{1}{4}\right)\right]^4 + 4\sum_{i=1}^{N}\left(\frac{3\lambda_i^2}{16} + \frac{\lambda_i}{8} - \frac{5}{16}\right)\sum_{j=1}^{N}\left(\frac{\lambda_j}{2} - \frac{1}{4}\right) - 3\left[\sum_{i=1}^{N}\left(\frac{\lambda_i}{2} - \frac{1}{4}\right)^2\right]^2$$

$$+3\left[\sum_{i=1}^{N}\left(\frac{\lambda_i^2}{4} - \frac{\lambda_i}{8} + \frac{3}{16}\right)\right]^2 - \sum_{i=1}^{N}\left(\frac{3\lambda_i^3}{8} - \frac{49\lambda_i}{128} - \frac{15}{32}\right)$$

$$\simeq \frac{1}{16}\left[\sum_{i=1}^{N}\left(\lambda_i - \frac{1}{2}\right)\right]^4 + \frac{1}{4}\sum_{i=1}^{N}\left(\frac{3\lambda_i^2}{2} + \lambda_i - \frac{5}{2}\right)\sum_{j=1}^{N}\left(\lambda_j - \frac{1}{2}\right) - \frac{3}{16}\left[\sum_{i=1}^{N}\left(\lambda_i - \frac{1}{2}\right)^2\right]^2$$

$$+\frac{3}{16}\left[\sum_{i=1}^{N}\left(\lambda_i^2 - \frac{\lambda_i}{2} + \frac{3}{4}\right)\right]^2 - \frac{1}{8}\sum_{i=1}^{N}\left(3\lambda_i^3 - \frac{49\lambda_i}{16} - \frac{15}{4}\right).$$

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