Far East Journal of Mathematical Sciences (FJMS)
Volume 59, Number 2, 2011, Pages 173-187
Available online at http://pphmj.com/journals/fjms.htm
Published by Pushpa Publishing House, Allahabad, INDIA

ON SELECTION OF MODELS FOR CONTINUOUS META ANALYSIS DATA WITH INCOMPLETE VARIABILITY MEASURES

Nik Ruzni Nik Idris and Norraida Sarudin

Department of Computational and Theoretical Sciences
International Islamic University Malaysia
Kuantan 25200, Pahang, Malaysia
e-mail: ruzni@iiu.edu.my
norraida@iiu.edu.my

Abstract

The choice between the fixed and random effects models for providing an overall meta analysis estimates may affect the accuracy of those estimates. When the study-level standard deviations (SDs) are not completely reported or are "missing" selection of a meta analysis model should be done with more caution. In this article, we examine through a simulation study, the effects of the choice of meta analysis model and the techniques of imputation of the missing SDs on the overall meta analysis estimates. The results suggest that imputation should be adopted to estimate the overall effect size, irrespective of the model used. However, the accuracy of the estimates of the corresponding standard error (SE) is influenced by the imputation techniques. For estimates based on the fixed effect model, mean

2010 Mathematics Subject Classification: 00A72, 81T80, 62P10, 62P25.

Keywords and phrases: meta analysis, fixed effect model, random effect model, missing SDs, imputation techniques.

This work was partially supported by the grant from IIUM Research Endowment Fund (Grant No: EDW B0802-106) of International Islamic University Malaysia.

Received August 19, 2011

imputation provides better estimates than multiple imputation, while those based on the random effects model are the more robust of the techniques imputation used.

1. Introduction

A meta analysis is a statistical technique for integrating quantitative results of the same research question from several sources. Theoretically, combining the results from multiple trials should enhance the precision and accuracy of any pooled results. In practice, however, there are a number of potential problems that may affect the validity of such results. One widely debated controversy related to meta analysis concerns the choice between a fixed and random effects model for providing an overall estimate of the effect size (Brockwell and Gordon [1], Whitehead [10]). When the difference in the effect sizes across the studies is due only to sampling error, they are considered homogeneous, and this source of variation can be accommodated in meta analysis by using the fixed effect model. However, if the variability in the effect size estimates exceeds those from sampling error alone, then a random effects model would be more appropriate as it takes into account the unexplained heterogeneity attributed by systematic differences between studies.

Another common problem with meta analysis and systematic reviews is that when variability measures, particularly the standard deviations (SDs), are not reported in the published report of the trials. A popular approach in handling this problem is through imputation of the missing SDs (Higgins and Thompson [4], Wiebe et al. [11]). Earlier studies which examined the effects of imputing the missing SDs on the overall meta analysis estimates (Furukawa et al. [3], Idris and Robertson [5], Thiessen et al. [9]) concluded that imputation recovers most of the lost information in the estimate of effect size and the corresponding SE. These studies, however, did not look at the effect of the model used to estimate the effect size and the corresponding SE.

This article investigates and compares, empirically, the effects of imputing the missing SDs and the choice of meta analysis model on the

overall meta analysis estimates. We used meta analysis estimates based on the fixed and random effect models obtained from three sets of simulated data, namely, (1) the complete data - where all studies are assumed to report the SDs (2) the incomplete data - where studies with missing SDs were excluded (3) the imputed data-where the missing SDs were imputed, and the studies with imputed SDs were included in the analysis. The effect estimates and their corresponding SE from (2) and (3) were compared to those based on (1). The imputation methods considered in this study is the weighted mean imputation and the multiple imputation (MI). These techniques of imputation were chosen as they are the most commonly adopted techniques in meta analyses particularly in psychology and social science (Whitehead [10]). The mean imputation has some popularity among the analysts due to its simplicity and ease of understanding and interpretation. Although this method is known to suffer from a reduction in variability for the variable as a constant value is substituted for all the missing variables, this technique is recommended if less than 10% of the data are missing (Idris and Robertson [5]). The MI is a popular choice of imputation technique and the main advantage is that it allows for the computation of the uncertainty due to missing values in addition to those due to sampling error.

2. Meta Analysis Model

The fixed effect model assumes that the true effect is homogeneous across studies and thus variation in the observed values is assumed to be due to random error. Suppose y_i is the estimated effect size for the *i*th study from a collection of *N* studies. A general fixed effect model is given by

$$y_i = \theta + \varepsilon_i, \tag{1}$$

where $\varepsilon_i \sim N(0, \sigma_i^2)$, $i = 1, 2, ..., N$ are the random deviations from the true effect size, θ, which are assumed to be independent with mean zero and variance σ^2. Thus the study specific variance is $V(y_i) = \sigma_i^2$. The overall estimate of the effect $\hat{\theta}$ and the corresponding variance of the estimate

$V(\hat{\theta})$ are

$$\hat{\theta} = \frac{\sum w_i y_i}{\sum w_i},$$

$$V(\hat{\theta}) = \frac{1}{\sum w_i}, \tag{2}$$

where $w_i = \frac{1}{V(y_i)} = \frac{1}{\sigma_i^2}$. The overall estimate of effect and its confidence interval therefore are specific to the trials included in the meta analysis and cannot be generalized to a larger population (Fleiss [2]).

In contrast to the fixed effect model, the random effects model does not assume a homogeneous treatment effect across studies, but assumes that the treatment in each trial is itself a realization of a random variable, which is usually assumed to be normally distributed. The random effect model incorporates a between-study random term, ν_i into the model where ν_i is assumed to be normally distributed with mean 0 and variance σ_ν^2 and is independent of the error terms ε_i. This gives

$$y_i^* = \theta_i + \varepsilon_i,$$

$$\theta_i = \theta + \nu_i,$$

where $\varepsilon_i \sim N(0, \sigma_i^2)$ and $\nu_i \sim N(0, \sigma_\nu^2)$, $i = 1, 2, ..., N$. The variance of the study specific estimate in this case is

$$V(y_i^*) = \sigma_i^2 + \sigma_\nu^2$$

and the overall estimate of the effect and the corresponding variance of the estimate for the random effect model are

$$\hat{\theta}^* = \frac{\sum w_i^* y_i^*}{\sum w_i^*},$$

$$V(\hat{\theta}^*) = \frac{1}{\sum w_i^*},$$

where the weight is given by $w_i^* = [\sigma_i^2 + \sigma_v^2]^{-1}$.

Consequently, the standard error of each trial estimate is increased due to the addition of this between-trial variation. By allowing the between-study variability to be accounted for in the overall estimate and in its standard error, the random effect model produces results which can be considered to be more generalizable and realistic in estimating treatment effect for a future study.

3. Method

3.1. Simulation of data

The data for each meta analysis are simulated using the random effects model described below

$$y_{ij} = \beta_{0i} + \beta_{1i} T_{ij} + \varepsilon_{ij},$$

where β_{0i} is the random study effect, T_{ij} represents the dummy covariates for treatment which takes two values, namely, 0 for the control and 1 for the treatment arm, and β_{1i} is the random treatment effect which is assumed to vary across the studies, but would take a fixed value under the fixed effect model, and ε_{ij} are the random error terms. y_{ij}, β_{0i}, β_{1i} and ε_{ij} are assumed to be independent and normally distributed with $\varepsilon_i \sim N(0, \sigma_\varepsilon^2)$; $\sigma_\varepsilon^2 = 1$; $\beta_{0i} \sim N(\beta_0, \sigma_{\upsilon 0}^2)$; $\beta_0 = 0$, $\sigma_{\upsilon 0}^2 = 1$; $\beta_{1i} \sim N(\beta_1, \sigma_{\upsilon 1}^2)$; $\beta_1 = 1$, $\sigma_{\upsilon 1}^2 = 1$. The number of patients in each study for each N are assumed to be equal, i.e., $n_i = n$ for $i = 1, 2, ..., N$, with equal number of patients undergoing the two treatments, i.e., $n_{0i} = n_{1i} = 1/2\, n$. The parameters varied cross the simulation are the number of studies in each meta-analysis (N) at 10, 20, 30; the number of patients within each study in a meta analysis (n) at 20, 60, 100; and the percentage of studies with missing SDs (x%) at 10, 30, 50. Each

of the 27 combinations of the number of studies N, the sample size n and the percentage of missing studies x%, were repeated 500 times, which is adequate as the differences in the estimates based on 500 and 750 simulations were small in majority of cases (less than 0.005). The mean effect estimate and the mean SE over the 500 simulations were computed. For multiple imputation, the computation of the SE of the estimates takes into account the variation due to imputation as described by Robertson et al. [7].

3.2. Creation of the missing SDs

To create the SDs missing completely at random, x% $(x = 10, 30, 50)$ studies were selected at random from N studies, and excluded from the data.

3.3. Imputation techniques

Mean imputation: The missing variances were replaced by the weighted mean of the available variances where the weight is number of patients in each study (n). In this case, however, the weight does not make much difference since n is assumed to be equal in each MA. This process was repeated 500 times for each missing value, which resulted in a set of 500 estimated effect sizes and the corresponding variances. The overall estimates of effect size were computed by taking the mean of the 500 effect sizes, while its overall variances were computed by taking the mean of 500 variances of the estimates.

Multiple Imputation: Each missing variance was replaced by a randomly selected value from the available variances and estimates based on this data recorded. For multiple imputation, this process was repeated 500 times in each of the 500 simulation run. This allows the uncertainty induced by the imputation to be incorporated into the overall estimate of the variance of the estimate, which is computed by adding the mean of the 500 variances of the estimate and the variance of the 500 effect sizes (Robertson et al. [7]).

3.4. Performance measures

The performance of the two imputation techniques for each model was evaluated using the percentage relative bias (PRB) between the estimates

which are based on all studies with no missing SDs and the corresponding estimates using studies with imputed SDs using the two techniques of imputation. The PRB for the effect size based on mean imputation, for instance will be computed as follows:

$$PRB = \frac{\left[\sum_{i=1}^{500} \frac{\hat{\theta}_{true} - \hat{\theta}_{impute}}{\hat{\theta}_{true}}\right]}{500} \times 100,$$

where $\hat{\theta}_{true}$ is the estimate of effect size based on all studies, $\hat{\theta}_{impute}$ is the effect size based on studies which includes the SDs imputed using the mean or multiple imputation and N is the number of simulations. Similar procedure is used for the computation of PRB in variances of the effect size estimate.

4. Result

4.1. Fixed effect model

The percentage relative bias (PRB) for the estimates based on the fixed effect model are tabulated in Table 1. Clearly the PRB in the SE of the estimates are much higher compared to those of the effect size. Furthermore, the PRB are generally smaller when the missing SDs are imputed compared to the approach of excluding the studies with missing SDs. The trends of the PRB in the effect estimates for the different values of x% are illustrated in Figure 1. There is not much difference in the magnitude of the PRB when the missing SDs are imputed using the two techniques of imputations. The mean imputation performs only slightly better than the MI. (Mean: 0.005%-0.07%; MI: 0.01%-0.3%).

As expected, the PRB in the SE of the estimates (Figure 2) are much more higher when the studies with missing SDs are excluded compared to when the missing SDs are imputed (> 300%). Furthermore, there are significant differences in the PRB for the two imputation techniques. The mean imputation performs far better than MI, particularly for the larger percentages of missing SDs (> 30%). Additionally, the percentage of studies

with missing SDs, *x*%, appears to have substantial impact on the PRB in SE, namely, the bias increases with *x*%. The trend is observed when the missing SDs are imputed as well as when studies are omitted.

Table 1. Fixed effect model: percentage relative bias in effect size and the SE of the effect size $(n = 60)$

X %	*N*	% Relative Bias of Effect Size			% Relative Bias of SE of Effect Size		
		OMIT	MI	MEAN	OMIT	MI	MEAN
10	10	0.16	0.02	0.05	–5.5	–2.40	–0.09
	20	–0.45	0.02	0.01	–5.4	–2.64	–0.11
	30	–0.21	0.03	–0.01	–5.4	–2.70	0.03
30	10	–0.14	0.03	–0.17	–19.7	–6.01	–0.21
	20	–0.01	–0.07	0.14	–19.5	–7.77	–0.20
	30	0.62	0.02	–0.06	–19.5	–7.90	–0.23
50	10	0.57	0.34	–0.01	–41.5	–10.5	–0.36
	20	–0.83	–0.06	0.02	–41.5	–12.3	–0.39
	30	–0.82	0.08	0.06	–41.3	–12.6	–0.27

OMIT: The PRB between estimates based on complete data and incomplete data.

MI: The PRB between estimates based on complete data and data with imputed SDs using the MI techniques.

MEAN: The PRB between estimates based on complete data and data with imputed SDs using the mean imputation.

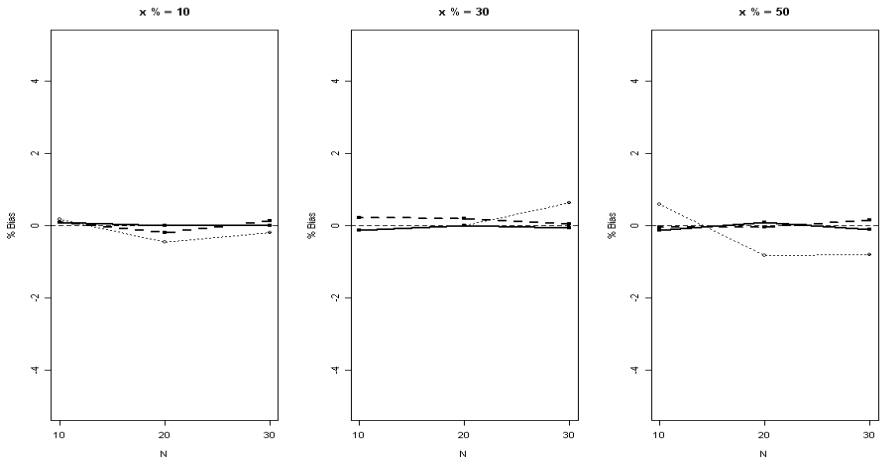

Figure 1. Fixed effect model: percentage relative bias in effect size $(n = 60)$. (Thin dotted-line: studies with missing SDs are omitted; thick break-line: mean imputation; thick solid-line: multiple imputation.)

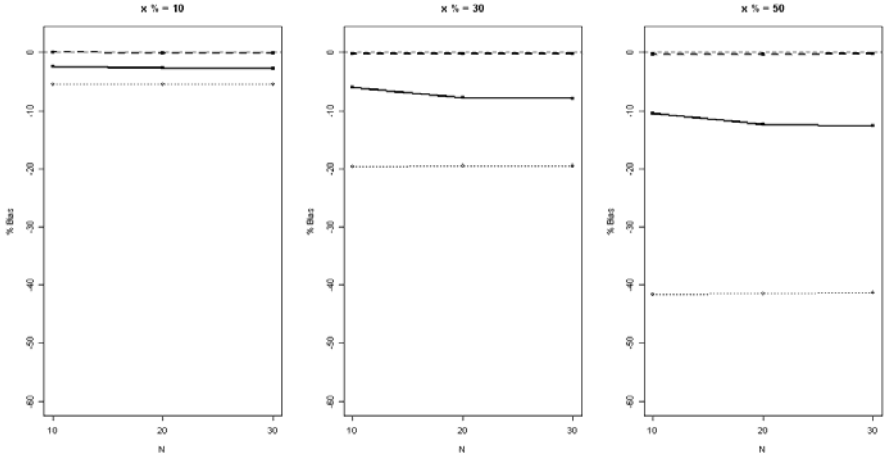

Figure 2. Fixed effect model: percentage relative bias in the SE of the effect size $(n = 60)$. (Thin dotted-line: studies with missing SDs are omitted; thick break-line: mean imputation; thick solid-line: multiple imputation.)

4.2. Random effect model

The PRB for the estimates that are based on the random effect model are presented in Table 2. Consistent with the results for the fixed effect model, the PRB are much smaller in the effect size compared those in the SE of the effect size. Additionally, the PRB are much larger if the studies with missing SDs are excluded, compared to those when the missing SDs are imputed. However, there are no notable differences in the magnitude of the PRB in the effect size using either the mean imputation or the MI (Figure 3).

In contrast, when studies with missing SDs are excluded, the PRB in the SE of the effect size increases significantly with increasing *x*%. In this case, the PRB increases up to 40% when half of the studies are excluded. However, imputation of the missing SDs appears to recover most of the information, as illustrated in Figure 4, where the relative biases are all very close to zero, for both techniques of imputation. This is different from the results obtained from estimates based on the fixed effect model, where mean imputation seems to be more superior in recovering the information on the SE of the estimates compared to the MI imputation. Additionally, when the SDs are imputed, the study sizes *n* and the percentage of missing SDs, *x*%, have little effect on the bias in SE.

Table 2. Random effect model: percentage relative bias in the effect size and the SE of the effect size $(n = 60)$

X %	N	% Relative Bias of Effect Size			% Relative Bias of SE of Effect Size		
		OMIT	MI	MEAN	OMIT	MI	MEAN
10	10	–0.19	0.012	0.007	–4.9	0.12	0.01
	20	0.30	–0.003	0.003	–5.4	0.01	0.01
	30	–0.29	0.0001	0.0002	–5.4	0.03	0.02
30	10	–0.13	–0.022	–0.007	–17.5	0.01	0.09
	20	0.54	–0.008	0.001	–19.0	0.01	0.02
	30	–0.83	–0.0001	–0.004	–19.1	0.02	0.02
50	10	–0.25	0.082	0.002	–35.8	0.03	0.40
	20	0.60	0.005	–0.005	–39.6	0.04	0.12
	30	–0.46	0.002	–0.006	–39.7	0.09	0.08

OMIT: The PRB between estimates based on complete data and incomplete data.

MI: The PRB between estimates based on complete data and data with imputed SDs using the MI techniques.

MEAN: The PRB between estimates based on complete data and data with imputed SDs using the mean imputation.

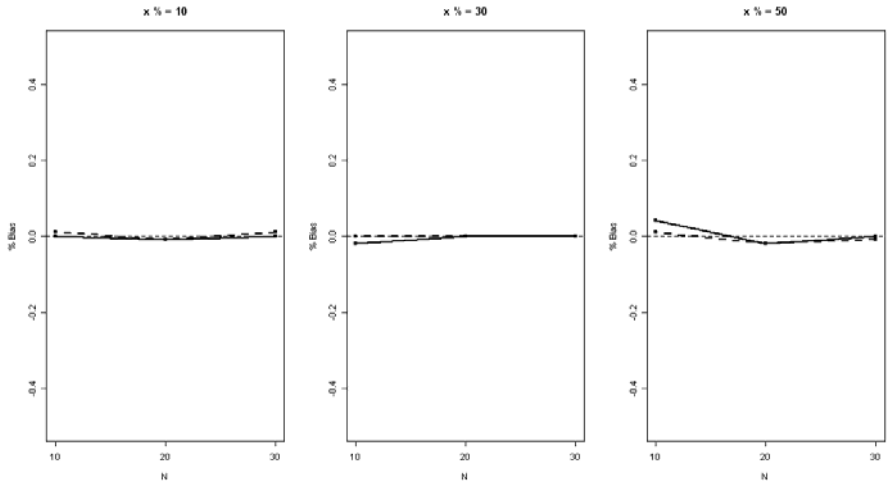

Figure 3. Random effect model: percentage relative bias in effect size $(n = 60)$. (Thick break-line: mean imputation; thick solid-line: multiple imputation.)

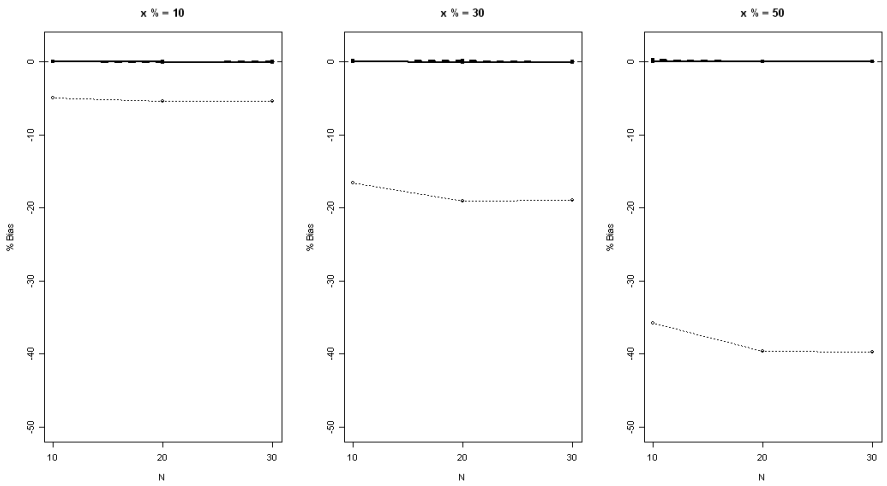

Figure 4. Random effect model: percentage relative bias in SE of the effect size $(n = 60)$. (Thin dotted-line: studies with missing SDs are omitted; thick break-line: mean imputation; thick solid-line: multiple imputation.)

5. Conclusions

In this paper, we investigated the influence of the choice of a meta analysis model and the imputation techniques on bias in the estimates of meta analysis parameters, namely, the treatment effect size and the corresponding SE, in continuous data with missing SDs in some of the studies included in the meta analysis. Comparisons in the form of PRB were made between the estimates based on the random effect model and the fixed effect model. The main conclusions drawn from this project support many of the findings in previous literature. We have additionally illustrated that regardless whether the estimates of overall effect size are based on the fixed or random effect model, imputation is a good approach in handling the problem of missing study-level SDs. The PRB produced using this approach is relatively smaller compared to excluding the studies with missing SDs. In fact, the expected bias in this case will tend to zero if the SDs across the studies are assumed to be completely homogeneous (Idris [6]). Nonetheless, while imputation of the missing SDs is recommended to estimate the effect size, it is not critically necessary as the biases introduced are generally not very substantial particularly when the percentage of missing SDs is below 10%.

In contrast, imputation is always recommended to estimate the SE of the effect size in data with missing SDs as otherwise serious bias may be introduced. The results show that if the random effect model is used to estimate the SE of the estimate in the data where there is some missing SDs, both the non-parametric MI and mean imputation will give equally good estimates (no difference in PRB; $p < 0.337$). On the other hand, if the estimate of the SE is based on the fixed effect model, then the techniques of imputation adopted will have some impact on the PRB introduced into the estimate of the SE. In this particular study, it is observed that if the fixed effect model is used, then mean imputation is expected to produce smaller PRB compared to those using the MI (difference; $p < 0.001$). These results are clearly illustrated in Figure 2.

Therefore, in deciding the imputation technique to employ for the missing SDs, an analyst should also consider the type of meta analysis model that the estimate is based on, in order to minimise the bias. It is noted that the random effect model is more robust to the type of imputations used. Additionally, in the random effect model, both the MI and mean imputation produced smaller PRB compared to those from the fixed effect model. Although the random effects model appears to be a safer choice, there are some concerns regarding its general application in practice such as the assumptions of normally distributed random effects or that poses problems in both its validity, and in our ability to check the validity for meta analyses based on small number of studies (Sutton et al. [8]).

It is clear that when the studies with missing SDs are excluded from the analysis, then the fixed or random effect models will generate about the same amount of bias in both the estimates of the effect size and its corresponding SE. Furthermore, this approach is not recommended for higher percentage of missing SDs. (> 10%) as the PRB could get as high as 40%.

In this study, we assumed that the study level SD is missing completely at random (MCAR). This implies that the recorded observed standard deviations are a random sample of the population of standard deviations from all studies. Although this assumption appears to be idealistic, it is a common approach in most meta analyses. In reality, however, the SDs are more likely

not to be missing with MCAR, but the non-reporting mechanism may be a function of either the SD itself (MAR - 'missing' at random), such as when studies may opt not to report the SDs because their values are large. Additionally, the non-reporting may also be dependent on other observed variables within the study (MNAR - 'missing' not at random), such as the study size, i.e., studies with smaller sample sizes are more likely not to report the standard deviations compared to those of larger sample size (Robertson et al. [7]).

These analyses are not intended to provide a specific guide for the model and imputation techniques to be utilised but to investigate their influence on the possible bias in the estimates of meta analysis parameters. However, we may suggest that when there are missing SDs, an analyst should look at the choice of model used before deciding on the technique of imputation to be employed. This study shows that if the FE is used, then mean imputation is recommended. The random effect model is, however, more robust and either the mean or MI technique is good. However, for this case, the MI is recommended as it takes into account the variations due to imputation.

References

[1] S. E. Brockwell and I. R. Gordon, A comparison of statistical method for meta-analysis, Stat. Med. 20 (2001), 825-840.

[2] J. L. Fleiss, Statistical basis of meta-analysis, Stat. Methods Med. Res. 2 (1993), 121-145.

[3] T. A. Furukawa, C. Barbui, A. Cipriani, P. Brambilla and N. Watanabe, Imputing missing standard deviations in meta analyses can provide accurate results, J. Clin. Epidemiol. 59 (2006), 7-10.

[4] J. P. T. Higgins and S. G. Thompson, Quantifying heterogeneity in meta analysis, Stat. Med. 21 (2002), 1539-1558.

[5] N. R. N. Idris and C. Robertson, The effects of imputing the missing standard deviations on the standard error of the meta analysis estimates, Comm. Statist. Simulation Comput. 38 (2009), 513-526.

[6] N. R. N. Idris, Estimating meta analysis parameters in non-standard data, Ph.D. Thesis, University of Strathclyde, 2006.

[7] C. Robertson, N. R. N. Idris and P. Boyle, Beyond classical meta analysis: can inadequately reported studies be included?, Drug Discovery Today 9 (2004), 924-931.

[8] A. J. Sutton, K. R. Abrams, D. R. Jones, T. A. Sheldon and F. Song, Missing data, Methods for Meta-analysis in Medical Research, John Wiley, New York, 2000, pp. 199-204.

[9] P. H. Thiessen, N. Barrowman and A. X. Garg, Imputing variance estimates do not alter the conclusions of a meta-analysis with continuous outcomes: a case study of changes in renal function after living kidney donation, J. Clin. Epidemiol. 60(3) (2007), 228-240.

[10] A. Whitehead, Meta-analysis of Controlled Clinical Trials, John Wiley, London, 2002.

[11] N. Wiebe, B. Vandermeer, R. W. Platt, T. P. Klassen, D. Moher and N. J. Barrowman, A systematic review identifies a lack of standardization in methods for handling missing variance data, J. Clin. Epidemiol. 59 (2006), 342-353.