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Correction methods for measurement error in epidemiologic research

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Measurement error in continuous endpoints of randomised trials: Problems and solutions

In randomised trials, continuous endpoints are often measured with some degree of error. This chapter explores the impact of ignoring measurement error, and proposes methods to improve statistical inference in the presence of measurement error. Three main types of measurement error in continuous endpoints are considered: classical, systematic and differential. For each measurement error type, a corrected effect estimator is proposed. The corrected estimators and several methods for confidence interval estimation are tested in a simulation study. These methods combine information about error-prone and error-free measurements of the endpoint in individuals not included in the trial (external validation sample). We show that when classical measurement error in continuous endpoints is ignored, the treatment effect estimator is unbiased, while Type-II error is increased at a given sample size. Conversely, the estimator can be substantially biased when measurement error is systematic or differential. In those cases, bias can largely be prevented and inferences improved upon using information from an external validation sample, of which the required sample size increases as the strength of the association between the error-prone and error-free endpoint decreases. Measurement error correction using already a small (external) validation sample is shown to improve inferences and could be considered in trials with error-prone endpoints. Implementation of the proposed correction methods is accommodated by a new software package for R.

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2.1. Introduction

In randomised controlled trials, continuous endpoints are often measured with some degree of error. Examples include trial endpoints that are based on self-report (e.g. self-reported physical activity levels [1]), endpoints that are collected as part of routine care (e.g. in pragmatic trials [2]), endpoints that are assessed without blinding the patient or assessor to treatment allocation (e.g., in surgical [3] or dietary [4] interventions) and an alternative endpoint assessment that substitutes a gold-standard measurement because of monetary or time constraints or ethical considerations (e.g. food frequency questionnaire as substitute for doubly-labelled water to measure energy intake [5]). In these examples, the continuous endpoint measurements contain error in the sense that the recorded endpoints do not unequivocally reflect the endpoint one aims to measure.

Despite calls for attention to the issue of measurement error in endpoints (e.g., [6]), developments and applications of correction methods for error in endpoints are still rare [7]. Specifically, methodology that allow for correction of study estimates for the presence of measurement error have so far largely been focused on the setting of error in explanatory variables, which may give rise to inferential errors such as regression dilution bias [8–13]. In addition, the application of correction methods for measurement error in the applied medical literature is unusual [9, 14].

We provide an exploration of problems and solutions for measurement error in continuous trial endpoints. For illustration of the problems and solutions for measurement error in continuous endpoints we consider one published trial that examined the efficacy and tolerability of low-dose iron-supplements during pregnancy [15]. To test the effect of the iron supplementation on maternal haemoglobin levels, haemoglobin concentrations were measured at delivery in venous blood.

This chapter describes a taxonomy of measurement error in trial endpoints, evaluates the impact of measurement error on the analysis of trials and tests existing and proposes new methods evaluating trials containing measurement error. Implementation of the proposed measurement error correction methods (i.e., the existing and novel methods) are supported by introducing a new R package *mecor*, available at: <https://github.com/LindaNab/mecor>. This chapter is structured as follows. In section 2.2 we revisit the example trial introduced in the previous paragraph. Section 2.3 presents an exploration of measurement error structures and their impact on inferences of trials. In section 2.4 measurement error correction methods are proposed. A simulation study investigating the efficacy of the correction methods is presented in section 2.5. Conclusions and recommendations resulting from this study are provided in section 2.6.

2.2. Illustrative example: measurement of haemoglobin levels

Makrides et al. [15] tested the efficacy of a 20-mg daily iron supplement (ferrous sulfate) on maternal iron status in pregnant women in a randomised, two-arm, double-blind, placebo-controlled trial. Respectively, 216 and 214 women were randomised to the iron supplement and placebo arm. At delivery, a 5-mL venous blood sample was collected from the women to assess haemoglobin levels as a marker for their iron status. Haemoglobin levels of women in the iron supplement arm were significantly higher than haemoglobin levels of women in the placebo arm (mean difference 6.9, 95% confidence interval (CI) (4.4; 9.3)). Haemoglobin concentrations were measured spectrophotometrically. Mean

haemoglobin values were 137 (standard deviation (SD) 3.2) g/L when measured by certified measurements, compared to mean 135 (SD 0.96) g/L when measured using the equipment used in the trial to measure haemoglobin levels. This might indicate small measurement error in the measured haemoglobin levels of the women in the trial. The authors did not discuss if and how the remaining measurement error could have affected their results.

In this domain, similar trials have been conducted in which the endpoint was assessed with lower standards. For instance, in field trials testing the effectiveness of iron supplementation, capillary blood samples instead of venous blood samples are often used to measure haemoglobin levels (e.g., [16]). While easier to measure, capillary haemoglobin levels are less accurate than venous haemoglobin levels [17]. We now discuss how measurement error in haemoglobin levels might affect trial inference, by assuming hypothetical differences between capillary and venous haemoglobin levels. Two additional illustrative example trials are discussed in section S2.1 of the supplementary material.

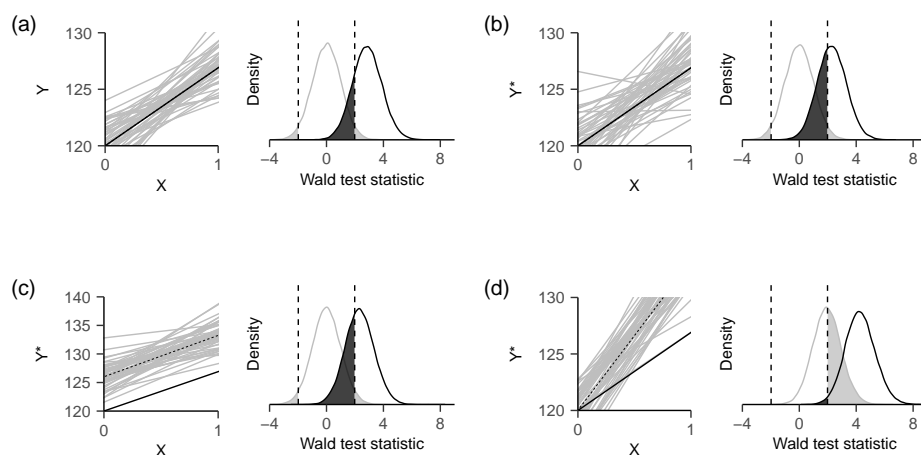


Figure 2.1: Illustration of impact of hypothetical measurement error in example trial 1 [15]: (a) no measurement error; (b) classical measurement error; (c) systematic measurement error; (d) differential measurement error. The left plots depict every thousandth estimated OLS regression line (grey lines), the average estimated treatment effect (dashed line) and the true effect (solid line). The right plots depict the density distribution of the Wald test-statistic of the slope of the regression line, under the null hypothesis of no effect (grey distribution) and the alternative hypothesis of any effect (black distribution).

2.2.1. Simulations based on example trial

We expand on the preceding example to hypothetical structures of error in measurement of the endpoints by simulation. These structures are only explained intuitively (explicit definitions are provided in section 2.3). For this example, we take the observed mean difference in haemoglobin levels in the two groups of the iron supplementation trials as a reference (6.9 g/L higher in the iron-supplemented group), and assume that haemoglobin levels are normally distributed with equal variance in both groups (SD 12.6 g/L). Fifty-thousand simulation samples were taken with 54 patients in each treatment arm. The number of patients differed from the 430 patients in the original trial to yield a Type-II

error of approximately 20% in the absence of measurement error at the usual alpha level (5%). Treatment effect for each simulation sample (mean difference in haemoglobin levels between the two arms) was estimated by OLS regression.

Classical measurement error in example trial. In the context of measurement of haemoglobin levels, random variability in the haemoglobin levels measured in capillary blood samples may be expected to vary more than haemoglobin levels measured in venous blood [17], independent of the true haemoglobin level and allocated treatment. Increased Type-II error is a well-known consequence of endpoints measured by the lower standard that are unbiased but more variable than the endpoints measured by the preferred measurement instruments [13]. This form of measurement error is commonly described as ‘random measurement error’ or ‘classical measurement error’ [10]. To simulate such independent variation, we arbitrarily increased the standard deviation of haemoglobin levels by 75% (from 12.6 to 22.05). This is equivalent to adding a term drawn from a normal distribution with mean 0 and standard deviation 18.1 to each endpoint. The impact of this imposed classical error was an increased between-replication variance of the estimated treatment effects of approximately 55% (left plot in panel b, Figure 2.1). The average estimated effect across simulations (depicted by the dashed line) is approximately equal to the true effect (depicted by the solid line), suggesting the classical measurement error did not introduce a bias in the estimated treatment effect (a formal proof is given in section Classical measurement error). Type-II error increased (to 38%) (grey area in Figure 2.1, panel b) while Type-I error remained at the nominal level (at 5%, illustrated by the red area in Figure 2.1, panel b).

Systematic measurement error in example trial. It may alternatively be assumed that capillary haemoglobin levels are systematically different from venous haemoglobin levels. This systematic difference can be either additive or multiplicative. For additive systematic measurement error, the capillary haemoglobin levels differ from venous haemoglobin levels with a certain constant, independently of venous haemoglobin levels. This implies that in both treatment groups mean haemoglobin level is higher, but that the difference between the two treatment groups is unbiased. The term systematic measurement error is often used to indicate multiplicative measurement error [18]. In that case, the expected capillary haemoglobin levels are equal to venous haemoglobin levels multiplied by a certain constant. Consequently, haemoglobin levels in capillary blood are more accurately measured in patients with low venous haemoglobin levels than in patients with high true haemoglobin levels (or vice versa). Under the assumption of a non-zero treatment effect, the expected difference between mean haemoglobin levels between the two treatment groups is biased; in the absence of a treatment effect, the expected difference between the two groups will remain unaffected. To simulate, we assumed that capillary haemoglobin levels are 1.05 times haemoglobin levels and we increased the standard deviation of haemoglobin levels by 75%, equivalent to the previous example. The impact of this imposed systematic measurement error structure is that the average treatment effect was biased, increasing from 6.9 to 7.2, and that there is an increased between-replication variance of the estimated treatment effect of approximately 66% (left plot in Figure 2.1, panel c). Type-II error increased (to 37%) (grey area in Figure 2.1, panel c) while Type-I error remained at rate close to nominal level (at 5%) (red area in Figure 2.1, panel c).

Differential measurement error in example trial. The measurement error structure may also differ between the treatment arms. In an extreme scenario, haemoglobin levels

in placebo group patients would be measured by venous blood samples while patients in active arm (iron supplemented) would be measured using capillary blood samples. To simulate such a scenario, we assume the same systematic error structure from the previous paragraph, now only applying to the active group. Additionally, we assume classical measurement error in the placebo group. This scenario classifies as differential measurement error [7]. The impact of this measurement error structure is that the average treatment effect was biased, increasing from 6.9 to 13.3, and that the between-replication variance of the estimated treatment effect is increased by approximately 62% (left plot in Figure 2.1, panel d). Type-II error decreased (to 0.1%) (grey area in Figure 2.1, panel d) and Type-I error rates increased (to 48%) (grey area in Figure 2.1, panel d).

2.3. Measurement error structures

Consider a two-arm randomised controlled trial that compares the effects of two treatments ($X \in \{0, 1\}$), where 0 may represent a placebo treatment or an active comparator. Let Y denote the true (or preferred) trial endpoint and Y^* an error prone operationalisation of Y . We will assume that both Y and Y^* are measured on a continuous scale. We assume a linear regression model for the endpoint Y :

$$Y = \alpha_Y + \beta_Y X + \varepsilon, \quad (2.1)$$

where ε is iid normally distributed with mean 0 and variance σ^2 . Under these assumptions and assumptions about the model for Y^* (described below), simple formulas for the bias in the OLS estimator of the treatment effect can be derived. Details of these derivations can be found in the supplementary material, section S2.2.

2.3.1. Classical measurement error

There is classical measurement error in Y^* when Y^* is an unbiased proxy for Y [10]: $Y^* = Y + e$, where e has mean 0 and $\text{Var}(e) = \tau^2$ and e independent of Y, X, ε in (2.1). Using Y^* instead of Y in the linear model yields:

$$Y^* = \alpha_Y^* + \beta_Y^* X + \delta, \quad (2.2)$$

Where $\beta_Y^* = \beta_Y$ and the residuals δ have mean 0 and variance $\sigma_\delta^2 = \sigma^2 + \tau^2$. This leads to a larger variance in $\hat{\beta}_Y^*$ (the estimator for β_Y^*) compared to the variance in $\hat{\beta}_Y$ (the estimator for β_Y). Consequently, classical measurement error will not lead to bias in the effect estimator but will increase Type-II for a given sample size.

2.3.2. Heteroscedastic measurement error

In the above we assumed that the variance in e is equal in both arms. When this assumption is violated, there is so called heteroscedastic measurement error. Heteroscedastic error will not lead to bias in the effect estimator, but will invalidate the estimator of the variance of $\hat{\beta}_Y^*$ (proof is given in supplementary material section S2.2).

2.3.3. Systematic measurement error

There is systematic measurement error in Y^* if Y^* depends systematically on Y : $Y^* = \theta_0 + \theta_1 Y + e$, where e has mean 0 and $\text{Var}(e) = \tau^2$ and e independent of Y, X, ε in (2.1).

Throughout, we assume systematic measurement error if $\theta_0 \neq 0$ or $\theta_1 \neq 1$ (and of course, $\theta_1 \neq 0$ in all cases). We assume independence between e and Y , X , ε in (2.1). Using Y^* with systematic measurement error in the linear model yields in the model defined by (2.2) where $\beta_Y^* = \theta_1 \beta_Y$ and the residuals δ have mean 0 and variance $\sigma_\delta = \theta_1^2 \sigma^2 + \tau^2$. Depending on the value of θ_1 , the variance of $\hat{\beta}_Y^*$ is larger or smaller than the variance of $\hat{\beta}_Y$. Hence, Type-II error will either decrease or increase under systematic measurement. Type-I error is unaffected since if $\beta_Y = 0$, $\beta_Y^* = 0$ (i.e., tests for null effects are still valid under systematic measurement error) (proof is given in supplementary material section S2.2).

2.3.4. Differential measurement error

There is differential measurement error in Y^* if Y^* depends systematically on Y varying for X : $Y^* = \theta_{00} + (\theta_{01} - \theta_{00})X + \theta_{10}Y + (\theta_{11} - \theta_{10})XY + e_X$, where e_X has mean 0 and $\text{Var}(e) = \tau_X^2$ and e_X independent of Y , and ε in (2.1) for $X = 0, 1$. Using Y^* with differential measurement error in the linear model yields in the model defined in (2.2) where $\beta_Y^* = \theta_{01} - \theta_{00} + (\theta_{11} - \theta_{10})\alpha_Y + \theta_{11}\beta_Y$ and the residuals δ have mean 0 and variance $[\theta_{10}^2 + (\theta_{11}^2 - \theta_{10}^2)X]\sigma^2 + \tau_X^2$ for $X = 0, 1$. Since the residual variance is not equal in both arms, the estimator of the variance of $\hat{\beta}_Y^*$ is invalid, and will underestimate the true variance. A heteroscedastic consistent estimator of the variance of $\hat{\beta}_Y^*$ is provided by the White estimator [19]. Assuming that the White estimator is used to estimate the variance of $\hat{\beta}_Y^*$, Type-I error is not expected the nominal level (α) and Type-II error will decrease or increase under the differential measurement error model (proof is given in supplementary material section S2.2).

2.4. Correction methods for measurement error in a continuous trial endpoint

In this section we describe several approaches to address measurement error in the trial endpoint. Throughout, we assume that Y^* is measured for all $i = 1, \dots, N$ randomly allocated patients in the trial. We also assume that Y and Y^* are both measured for a smaller set of different individuals not included in the trial ($j = 1, \dots, K$, $K < N$), hereinafter referred to as the external calibration sample. In all but one case, it is assumed that only Y^* and Y are measured in the external validation sample. In the case that the error in Y^* is different for the two treatment groups, it is assumed that the external validation sample is in the form of a small pilot study where both treatments are allocated (i.e., Y^* and Y are both measured after assignment of X). Instead of external validation data, we could use internal validation data to correct for measurement error (Y and Y^* are both measured in a small subset of the trial), which is not considered in this section as it was studied elsewhere [7].

A well-known consequence of classical measurement error in a continuous trial endpoint is that a larger sample size (as compared to the same situations without the measurement error) is needed to compensate for the reduced precision [13]. For example, the new sample size N^* may be calculated by N/R formula where R is the reliability coefficient and N the original sample size for the trial [20]. For solutions for heteroscedastic measurement error, we refer to standard theory of dealing with heteroscedastic errors in regression to find an unbiased estimator for the variance of $\hat{\beta}_Y$. (e.g., see [19] for an overview of different heteroscedasticity consistent covariance matrices).

Hereinafter we focus on measurement error in Y^* that is either systematic or differential, both of which have been shown to introduce bias in the effect estimator if measurement error is neglected (section 2.3). Consistent estimators for the intervention effects are introduced, and various methods for constructing CIs for these estimators are discussed. Section S2.3 in the supplementary material provides an explanation of the results stated in this section. Throughout, we assume that Y^* is measured for all $i = 1, \dots, N$ patients in the trial. We also assume that Y and Y^* are both measured for a smaller set of different individuals not included in the trial ($j = 1, \dots, K, K < N$), hereinafter referred to as the external validation sample. For an earlier exploration of the use of an internal validation set when there is systematic or differential measurement error in endpoints, see [7].

2.4.1. Systematic measurement error

From section Systematic measurement error it follows that natural estimators for α_Y and β_Y are

$$\hat{\alpha}_Y = (\hat{\alpha}_{Y^*} - \hat{\theta}_0)/\hat{\theta}_1 \quad \text{and} \quad \hat{\beta}_Y = \hat{\beta}_{Y^*}/\hat{\theta}_1, \quad (2.3)$$

Where $\hat{\theta}_0$ and $\hat{\theta}_1$ are the estimated error parameters from the validation data set using standard OLS regression. From equation (2.3), it becomes apparent that $\hat{\theta}_1$ needs to be assumed bounded away from zero for finite estimates of $\hat{\alpha}_Y$ and $\hat{\beta}_Y$ [8]. The estimators in (2.3) are consistent, see for a proof section S2.3 in the supplementary material.

The variance of the estimators defined in (2.3) can be approximated using the Delta method, the Feller method, the Zero-variance method [21] and by bootstrap [22]. Further details are provided in section S2.3 of the supplementary material.

2.4.2. Differential measurement error

From section Differential measurement error it follows that natural estimators for α_Y and β_Y are,

$$\hat{\alpha}_Y = (\hat{\alpha}_{Y^*} - \hat{\theta}_{00})/\hat{\theta}_{10} \quad \text{and} \quad \hat{\beta}_Y = (\hat{\beta}_{Y^*} + \hat{\alpha}_{Y^*} - \hat{\theta}_{01})/\hat{\theta}_{11} - \hat{\alpha}_Y, \quad (2.4)$$

where $\hat{\theta}_{00}$, $\hat{\theta}_{10}$, $\hat{\theta}_{01}$ and $\hat{\theta}_{11}$ are estimated from the external validation set using standard OLS estimators. Here it is assumed that both $\hat{\theta}_{10}$ and $\hat{\theta}_{11}$ are bounded away from zero (for reasons similar to those mentioned in section 2.4.1). The estimators in (2.4) are consistent, see for a proof section S2.3 of the supplementary material. The variance of the estimators defined in (2.4) can be approximated using the Delta method [21], the Zero-variance method and by bootstrap [22]. Further details are provided in section S2.3 of the supplementary material.

2.5. Simulation study

The finite sample performance of the measurement error corrected estimators of the treatment effect was studied by simulation. We focussed on the setting of a two-arm trial in which the continuous surrogate endpoint Y^* was measured with systematic or differential measurement error, and in which an external validation set was available, which was varied in size. The results from example trial 1 are used to motivate our simulation study (see section 2.2).

2.5.1. Data generation

Data were generated for a sample of $N = 400$ individuals, approximately equal to the size of example trial 1 [15]. The individuals were equally divided in the two treatment arms. The true endpoints were generated according to model (2.1), assuming iid normal errors, and using the estimated characteristics found in example trial 1 ($\alpha_Y = 120$, $\beta_Y = 6.9$ and $\sigma = 12.6$). Surrogate endpoints Y^* were generated under models for systematic measurement error and differential measurement error described in section Systematic measurement error and Differential measurement error, respectively.

For systematic measurement error in Y^* , we set $\theta_0 = 0$ and $\theta_1 = 1.05$. Under the differential measurement error model we set $\theta_{00} = 0$, $\theta_{01} = 0$, $\theta_{10} = 1$, $\theta_{11} = 1.05$. We considered three scenarios based on the coefficient of determination between the Y^* and Y , $R_{Y^*,Y}^2$: (i) $R_{Y^*,Y}^2 = 0.8$, (ii) $R_{Y^*,Y}^2 = 0.5$ and (iii) $R_{Y^*,Y}^2 = 0.2$. This large range in coefficient of determination values reflects the wide variation we anticipate in practice from very strong correlations between Y^* and Y ($R_{Y^*,Y}^2 = 0.8$) to weak correlations ($R_{Y^*,Y}^2 = 0.2$), as for example, one could expect in the context of trials with dietary intake as endpoints [7, 23]. For $R_{Y^*,Y}^2 = 0.8$, $\tau = 6.6$ for systematic measurement error and $\tau_0 = 6.3$ and $\tau_1 = 6.6$ for differential measurement error. For $R_{Y^*,Y}^2 = 0.5$, $\tau = 13.2$ for systematic measurement error and $\tau_0 = 12.6$ and $\tau_1 = 13.2$ for differential measurement error. For $R_{Y^*,Y}^2 = 0.2$, $\tau = 26.5$ for systematic measurement error and $\tau_0 = 25.2$ and $\tau_1 = 26.5$ for differential measurement error. Additionally, we considered a scenario with greater systematic measurement error holding $\theta_0 = 0$ and $\theta_1 = 1.25$. Here, we only studied a high coefficient of determination $R_{Y^*,Y}^2 = 0.8$, implying that $\tau = 7.9$.

For the scenarios with systematic measurement error induced, a separate validation set was generated of size K with the characteristics of the placebo arm for each simulated data set. For differential measurement error scenarios, a validation data set was generated of size K for each simulated data set, with $K_0 = K_1 = K/2$ subjects equally divided over the two treatment groups. The sample size of the external validation data set (K) was varied with $K \in \{5, 7, 10, 15, 20, 30, 40, 50\}$ for systematic measurement error and $K \in \{10, 20, 30, 40, 50\}$ for differential measurement error.

2.5.2. Computation

For each simulated data set the corrected treatment effect estimator (2.3) for systematic error and (2.4) for differential error were applied. In systematic measurement error scenarios, 95% CIs for the corrected estimator were constructed by using the Zero-variance method, the Delta method, the Fieller method, and bootstrap based on 999 replicates (as defined in section Systematic measurement error). In the case of differential measurement error, 95% CIs for the corrected estimator were constructed by using the Zero-Variance method, the Delta method and the bootstrap based on 999 replicates (as defined in section Differential measurement error). The HC3 heteroscedastic consistent variance estimator was used to accommodate for heteroscedastic error in the differential measurement error scenario [19]. Furthermore, for both the systematic and differential measurement error scenarios the naive analysis was performed (resulting in a naive effect estimate and naive CI), which is the 'regular' analysis which would be performed if measurement error was neglected.

We studied performance of the corrected treatment effect estimators in terms of

percentage bias [24], empirical standard error (EmpSE) and square root of the mean squared error (SqrtMSE) [25]. The performance of the methods for constructing the CIs was studied in terms of coverage and Type-II error [25].

In our simulations, the Fieller method resulted in undefined CIs if in an iteration $\hat{\theta}_1 / \sqrt{t^2 / S_{yy}^{(c)}} > t_{N-2}$. The percentage of iterations for which the Fieller method failed to construct CIs is reported. If the Fieller method resulted in undefined CIs in more than 5% of cases in one simulation scenario, the coverage and average CI width were not calculated as this would result in unfair comparisons between the different CI constructing methods. The bootstrap CIs were based on less than 999 estimates in case the sample drawn from the external validation set consisted of K equal replicates. These errors occurred more frequently for small values of K and low R-squared. All simulations were run in R version 3.4, using the R package mecor (version 0.1.0). The results of the simulation are available at doi:10.6084/m9.figshare.7068695 and the code is available at doi:10.6084/m9.figshare.7068773, together with the seed used for the simulation study.

2.5.3. Results of simulation study

Systematic measurement error. Table 2.1 shows percentage bias, EmpSE and SqrtMSE of the naive estimator and the corrected estimator when there is systematic measurement error. Naturally, the percentage of bias in the naive estimator is about 5% if $\theta_1 = 1.05$ and 25% if $\theta_1 = 1.25$. For the corrected estimator and $\theta_1 = 1.05$ or $\theta_1 = 1.25$ and $R_{Y,Y}^2 = 0.8$, percentage bias, EmpSE and SqrtMSE of $\hat{\beta}_Y$ were reasonably small for $K \geq 10$. SqrtMSE of the corrected estimator was never lower than the SqrtMSE of the naive estimator because the bias in the naive estimator was small for $\theta_1 = 1.05$. However, for settings where bias in the naive estimator was greater ($\theta_1 = 1.25$), SqrtMSE of the corrected estimator was smaller than SqrtMSE of the naive estimator for $K \geq 15$. For the corrected estimator and $\theta_1 = 1.05$ and $R_{Y,Y}^2 = 0.5$, bias was reasonably small for $K \geq 30$. Nevertheless, SqrtMSE of the corrected estimator was always greater than SqrtMSE of the naive estimator. For the corrected estimator and $\theta_1 = 1.05$ and $R_{Y,Y}^2 = 0.2$, the bias of $\hat{\beta}_Y$ fluctuated and EmpSE and SqrtMSE was large for all K 's. Figure 2.2 shows the estimates of the intervention effect using the corrected estimator of each 10th iteration of our simulation, which provides a clear visualisation of the results formerly discussed. The larger the sample size of the external calibration set and the higher R-squared, the better the performance of the corrected estimator. The sampling distribution of $\hat{\theta}_1$ depicted in Figure 2.3 explains why there was so much variation in the corrected effect estimator for small sample sizes of the external validation set and low R-squared. Namely, for a number of iterations in our simulation, $\hat{\theta}_1$ was estimated close to zero, expanding the corrected estimator the same number of times resulting in large bias, EmpSE and MSE. Note that if $\hat{\theta}_1 < 0$, the sign of the corrected estimator changes, explaining why the corrected estimate of the intervention effect was sometimes below zero.

For $R_{Y,Y}^2 = 0.8$ and both $\theta_1 = 1.05$ and $\theta_1 = 1.25$, the Fieller method failed to construct CIs in 15, 5, 1 and 0.1 % of simulated datasets for respectively $K = 5, 7, 10, 15$. Therefore, coverage and average CI width of the Fieller method was not evaluated for $K \in \{5, 7\}$. For $R_{Y,Y}^2 = 0.5$, the Fieller method failed to construct CIs in 48, 36, 22, 8, 3, 0.3 % of simulated data sets for $K \in \{5, 7, 10, 15, 20, 30\}$, respectively. Consequently, coverage and average CI width was not evaluated for $K \in \{5, 7, 10, 15\}$. For $R_{Y,Y}^2 = 0.2$, the Fieller method

failed to construct CIs in 74, 71, 64, 53, 43, 26, 15 and 8 % of simulated data sets for $K \in \{5, 7, 10, 15, 20, 30, 40, 50\}$, respectively. the Fieller method was therefore not evaluated for $R_{Y^*, Y}^2 = 0.2$.

Table 2.2 shows coverage of the true intervention effect in the constructed CIs using the Zero-variance, Delta, Fieller method and bootstrap. Using Wald CIs for the naive effect estimator nearly yielded 95% coverage of the true treatment effect of 6.9, because for $\theta_1 = 1.05$ the bias percentage in the naive estimator was small (, 5%). Yet, as bias percentage increased in the naive estimator for $\theta_1 = 1.25$ (i.e., 25%) coverage dropped to 83.5%. Table 2.3 shows average CI width using the Zero-variance, Delta and bootstrap. The Zero-variance method yielded too narrow CIs for all scenario's, an intuitively clear result as the Zero-variance method neglects the variance in $\hat{\theta}_1$. For $R_{Y^*, Y}^2 = 0.8$ the Delta, Fieller and bootstrap constructed correct CIs for $K \geq 15$. For $K \leq 10$ the Delta method and the Fieller method constructed too narrow CIs, and bootstrap too broad CIs. For $R_{Y^*, Y}^2 = 0.5$ the Delta and bootstrap constructed correct CIs for $K \geq 30$. For $K \leq 20$ the Delta method constructed too narrow CIs, and bootstrap too broad CIs. Coverage of the Fieller method was about the desired 95% level for $K \geq 30$.

Using the naive effect estimator, Type-II error was 0.2%, 2.9% and 31.6% for $R_{Y^*, Y}^2 = 0.8$ (both for $\theta_1 = 1.05$ and $\theta_1 = 1.25$), $R_{Y^*, Y}^2 = 0.5$ and $R_{Y^*, Y}^2 = 0.2$, respectively. Type-II error in the corrected estimator using the Zero-variance and Delta method and bootstrap was 0%. For the considered scenario's using the Fieller method, Type-II error was 0.02% for $R_{Y^*, Y}^2 = 0.8$ and 2.9% for $R_{Y^*, Y}^2 = 0.5$.

Table 2.1: Percentage bias, Empirical Standard Error (EmpSE) and Squared root of Mean Squared Error (SqrtMSE) of the naive estimator and the corrected estimator for systematic measurement error ($\theta_0 = 0$ and $\theta_1 = 1.25$ or $\theta_1 = 1.05$), R-squared equal to 0.8, 0.5 and 0.2 and, different sample sizes of the validation data set. Each scenario is based on 10,000 replicates, the value of the estimand is 6.9, based on example trial 1 by Makridakes et al. [15]

Performance Measure ^a	θ_1	$R_{Y,X}^2$	Naive Estimator	Corrected Estimator															
				Sample Size					External Calibration Set										
				5	7	10	15	20	30	40	50								
Percentage bias (%)	1.25	0.8	24.9	88.9	29.0	3.7	2.0	1.6	0.9	0.7	0.4								
	1.05	0.8	4.9	88.9	29.0	3.7	2.0	1.6	0.9	0.7	0.4								
		0.5	4.9	55.3	57.5	-2.4	7.6	5.8	4.3	3.0	2.0								
EmpSE		0.2	4.9	168.2	-62.6	98.8	33.4	-142.2	-28.3	23.9	14.6								
	1.25	0.8	1.8	524.8	139.1	3.0	1.9	1.7	1.6	1.5	1.5								
SqrtMSE	1.05	0.8	1.5	524.8	139.1	3.0	1.9	1.7	1.6	1.5	1.5								
		0.5	1.9	267.0	329.1	83.7	14.4	11.0	2.5	2.3	2.1								
		0.2	3.0	1131.2	210.8	723.2	462.2	1044.4	225.5	70.5	24.8								
SqrtMSE	1.25	0.8	2.5	524.8	139.1	3.1	1.9	1.7	1.6	1.5	1.5								
	1.05	0.8	1.5	524.8	139.1	3.1	1.9	1.7	1.6	1.5	1.5								
		0.5	1.9	267.0	329.1	83.7	14.4	11.0	2.5	2.3	2.1								
		0.2	3.0	1131.2	210.8	723.1	462.2	1044.4	225.5	70.5	24.8								

^a Monte Carlo standard errors of Bias, EmpSE and MSE are $\text{EmpSE} \cdot \sqrt{1/10,000}$; $\text{EmpSE} \cdot (2 \cdot \sqrt{9,999})$; $\sqrt{\frac{\sum_{i=1}^{10,000} (\hat{\beta}_i - 6.9)^2 - \text{MSE}}{9,999 \cdot 10,000}}$, respectively [25].

Table 2.2: Confidence interval (CI) coverage of the naive estimator and the corrected estimator for systematic measurement error ($\theta_0 = 0$ and $\theta_1 = 1.25$ or $\theta_1 = 1.05$), R-squared equal to 0.8, 0.5 and 0.2 and, different sample sizes of the validation data set. Each scenario is based on 10,000 replicates; the value of the estimand is 6.9, based on example trial 1 by Makrides et al. [15]

θ_1	$R^2_{x,y}$	Naive Estimator ^a	Method for Construction of CI	Corrected Estimator									
				5	7	10	15	20	30	40	50		
1.25	0.8	83.5	Zero-Variance	70.3	74.0	77.4	80.3	82.8	84.4	85.3	86.3		
			Delta	93.8	95.3	95.7	95.9	96.0	96.0	95.9	95.7		
			Fieller ^b	-	-	94.5	94.7	95.0	95.3	95.2	95.0		
	0.5	94.6	Zero-Variance	95.9	96.1	95.5	94.9	94.8	95.0	95.1	94.8		
			Delta	77.8	81.3	84.4	87.1	89.2	90.9	92.0	92.2		
			Fieller ^b	92.1	93.9	94.3	94.8	95.1	95.3	95.4	95.2		
1.05	0.8	94.6	Zero-Variance	-	-	94.5	94.7	95.0	95.3	95.2	95.0		
			Delta	-	-	94.5	94.7	95.0	95.3	95.2	95.0		
			Fieller ^b	95.9	96.1	95.5	94.9	94.8	95.0	95.1	94.8		
	0.5	94.8	Zero-Variance	69.1	73.5	78.1	81.7	84.5	87.5	88.7	89.9		
			Delta	89.7	92.0	92.9	93.9	94.3	95.2	95.4	95.3		
			Fieller ^b	-	-	94.5	95.2	95.2	95.0	94.8	94.9		
0.2	95.1	Zero-Variance	93.9	95.9	96.3	95.8	95.4	94.8	94.8	94.8			
		Delta	57.1	64.5	71.0	76.8	80.3	84.3	86.0	87.6			
		Fieller ^b	86.8	89.7	90.9	92.2	93.5	94.4	94.6	94.9			
			Zero-Variance	-	-	89.8	93.2	94.9	95.8	95.8	95.7		
			Delta	-	-	89.8	93.2	94.9	95.8	95.8	95.7		
			Fieller ^b	88.9	93.8	95.5	96.4	96.7	96.8	96.8	96.1		

Monte Carlo standard errors of Coverage are $\sqrt{(\text{Coverage} \times (1 - \text{Coverage})) / 10,000}$ [25].

^a Coverage of the true intervention effect using regular Wald CIs of the naive effect estimator.

^b Results of the Fieller method are shown if less than 5% of cases resulted in undefined CIs (see section Computation).

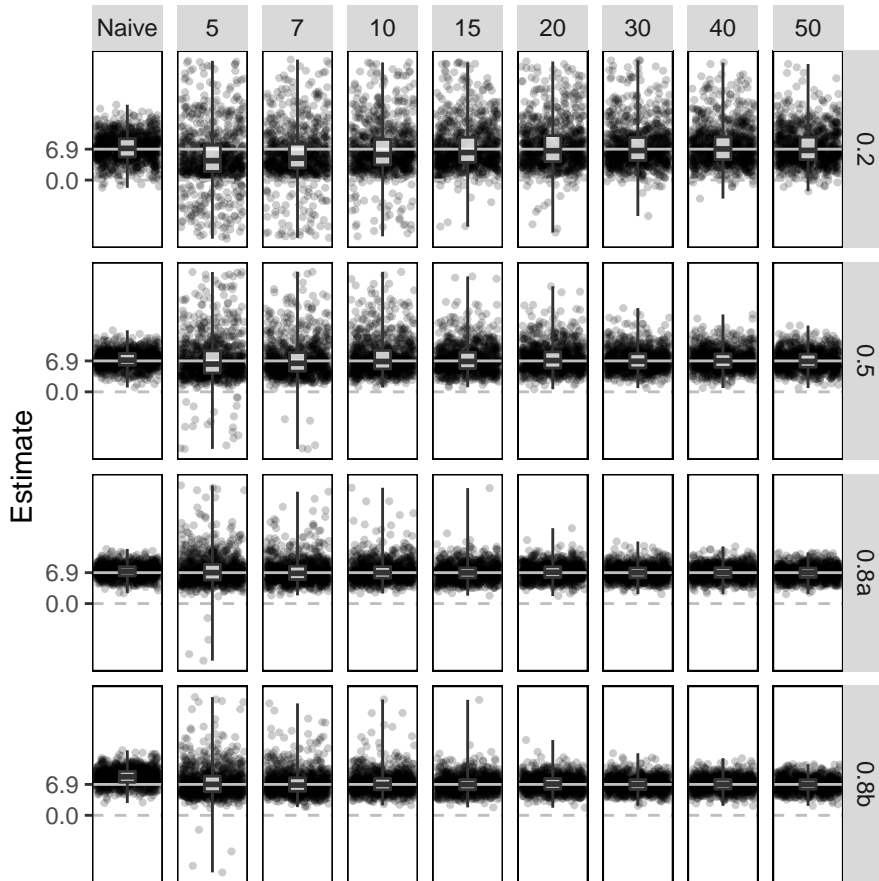


Figure 2.2: Estimates of the treatment effect using the naive estimator and corrected estimator for different values of R-squared (row grids) and different sample sizes of the external validation set (column grids) under systematic measurement error ($\theta_1 = 1.05$ (0.2; 0.5; 0.8a) or $\theta_1 = 1.25$ (0.8b)). Each grid is based on every 10th estimate of a simulation of 10,000 replicates, using an estimand of 6.9 (indicated by the solid supplementary material line), based on example trial 1 by Makridis et al. [15].

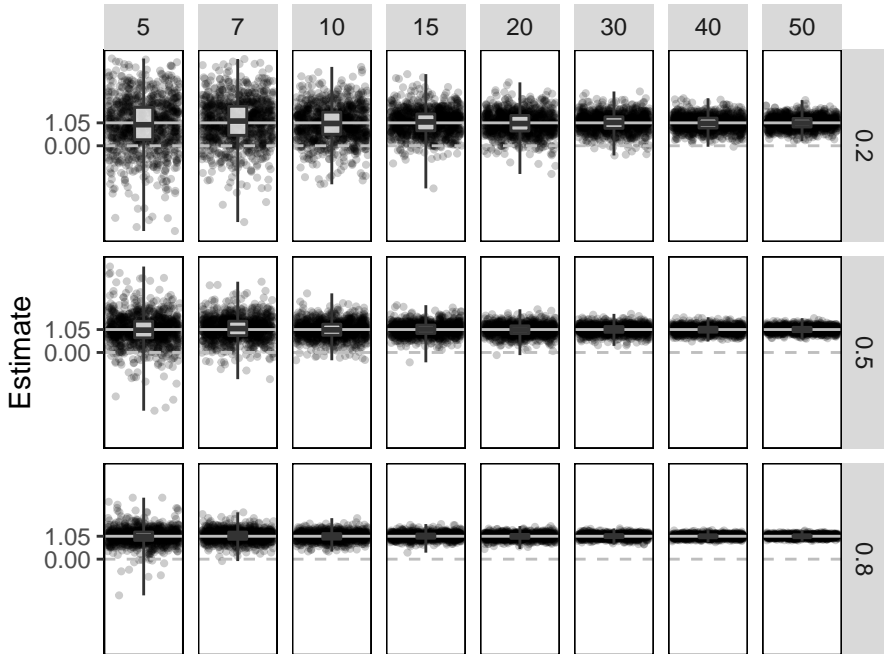


Figure 2.3: Estimates of θ_1 (i.e., slope of the systematic measurement error model) for different values of R-squared (row grids) and different sample sizes of the external validation set (column grids). Each grid is based on every 10th estimate of a simulation of 10,000 replicates, using an estimand of 1.05 (indicated by the solid supplementary material line).

Table 2.3: Average confidence interval (CI) width of the naive estimator and the corrected estimator for systematic measurement error ($\theta_0 = 0$ and $\theta_1 = 1.25$ or $\theta_1 = 1.05$), R-squared equal to 0.8, 0.5 and 0.2 and, different sample sizes of the validation data set. Each scenario is based on 10,000 replicates, the value of the estimand is 6.9, based on example trial 1 by Makrides et al. [15]

θ_1	$R^2_{X,Y}$	Naive Estimator ^a	Method for Construction of CI	Corrected Estimator										
				5	7	10	15	20	30	40	50			
1.25	0.8	6.9	Zero-Variance	30 333.0	1141.5	5.5	4.7	4.7	4.7	4.7	4.6	4.5	4.5	
			Delta	40.7	13.6	8.7	7.5	7.0	7.0	6.5	6.3	6.1	6.1	
			Fieller ^b	-	-	11.8	8.3	7.0	7.0	6.4	6.1	6.0	6.0	
			Bootstrap	86.9	29.3	14.1	8.3	7.1	7.1	6.4	6.1	6.0	6.0	
1.05	0.8	5.8	Zero-Variance	36 110.7	1359.0	6.5	5.6	5.5	5.5	5.4	5.4	5.4	5.4	
			Delta	35.0	12.2	8.0	7.0	6.7	6.7	6.3	6.1	6.0	6.0	
			Fieller ^b	-	-	11.8	8.3	7.0	7.0	6.4	6.1	6.0	6.0	
			Bootstrap	86.9	29.3	14.1	8.3	7.1	7.1	6.4	6.1	6.0	6.0	
	0.5	7.4	Zero-Variance	7228.9	9759.5	763.1	37.5	17.8	17.8	7.7	7.3	7.1	7.1	
			Delta	58.1	43.2	21.2	12.6	11.0	11.0	9.3	8.7	8.4	8.4	
			Fieller ^b	-	-	67.9	63.2	25.0	25.0	12.4	9.8	9.0	9.0	
			Bootstrap	146.8	87.4	65.2	34.7	22.8	22.8	12.4	9.9	9.0	9.0	
	0.2	11.6	Zero-Variance	126 830.3	11 677.5	87 123.4	30 709.4	324 870.7	12 430.8	774.6	126.8	126.8	126.8	
			Delta	179.3	102.5	112.7	69.9	65.7	34.1	19.7	16.6	16.6	16.6	
			Fieller ^b	-	-	92.6	95.1	72.1	82.2	60.6	59.2	59.2	59.2	
			Bootstrap	176.0	121.9	126.2	118.7	107.7	77.6	54.8	39.7	39.7	39.7	

^a Average CI width using regular Wald CIs of the naive effect estimator.

^b Results of the Fieller method are shown if less than 5% of cases resulted in undefined CIs (see section Computation).

Differential measurement error. Table 2.4 shows percentage bias, EmpSE and SqrtMSE of the naive estimator and the corrected estimator when there is differential measurement error. The percentage bias in the naive estimator was about 92%. For the corrected estimator and $R_{Y^*,Y}^2 = 0.8$, percentage bias, EmpSE and SqrtMSE of $\hat{\beta}_Y$ were reasonably small for $K \geq 20$. For the naive estimator and $R_{Y^*,Y}^2 = 0.5$, percentage bias, EmpSE and MSE of the corrected estimator were small for $K = 50$. For the naive estimator and $R_{Y^*,Y}^2 = 0.2$, percentage bias, EmpSE and MSE of the corrected estimator was large for all K 's. The estimates of the intervention effect using the corrected estimator of each 10th iteration of our simulation is shown in Figure 2.4, which provides a clear visualization of the results formerly discussed. the sample size of the external validation set and the higher R-squared, the better the performance of the corrected estimator.

Table 2.5 shows coverage of the true intervention effect in the constructed CIs and average CI width using the Zero-Variance and Delta method and bootstrap. Coverage of the true treatment effect of 6.9 using Wald CIs for the naive effect estimator were about 1%, 7% and 41% for $R_{Y^*,Y}^2 = 0.8$, $R_{Y^*,Y}^2 = 0.5$ and $R_{Y^*,Y}^2 = 0.2$, respectively. In all cases, the Zero-Variance method yielded too narrow CIs; the Delta method yielded too broad CIs and the bootstrap yielded mostly too broad CIs, except for $R_{Y^*,Y}^2 = 0.8$ and $K = 30$ and $K = 40$ (too narrow). For $R_{Y^*,Y}^2 = 0.8$ and $K = 50$, coverage of the true intervention effect was 95%.

Type-II error in the naive effect estimator was 0%, 0% and 0.4% for $R_{Y^*,Y}^2 = 0.8$, $R_{Y^*,Y}^2 = 0.5$ and $R_{Y^*,Y}^2 = 0.2$, respectively. Type-II error in the corrected effect estimator using the Zero-variance and Delta method and bootstrap was 0%.

Table 2.4: Percentage bias, Empirical Standard Error (EmpSE), Mean Squared Error (MSE), Squared root of Mean Squared Error (SqrtMSE) of the corrected estimator for differential measurement error ($\theta_{00} = 0, \theta_{10} = 1, \theta_{01} = 0, \theta_{11} = 1.05$) R-squared equal to 0.8, 0.5 and 0.2 and different sample sizes of the validation data set. Each scenario is based on 10,000 replicates, the value of the estimand is 6.9, based on example trial 1 by Makrides et al. [15]

Performance Measure ^a	$R_{Y^*,Y}^2$	Naive Estimator	Corrected Estimator				
			Sample Size External Calibration Set				
			10	20	30	40	50
Percentage bias (%)	0.8	91.8	5.2	1.2	-0.4	-0.2	-0.1
	0.5	91.8	-9.7	33.0	154.2	-21.4	-0.1
	0.2	91.9	-319.4	152.9	193.1	-21.5	2.2
EmpSE	0.8	1.4	52.0	6.8	2.9	2.6	2.3
	0.5	1.8	949.1	369.1	1080.4	142.1	4.5
	0.2	2.9	2658.0	8425.8	1569.7	443.7	92.1
SqrtMSE	0.8	6.5	52.0	6.8	2.9	2.6	2.3
	0.5	6.6	949.1	369.1	1080.4	142.1	4.5
	0.2	7.0	2658.0	8425.4	1569.7	443.7	92.1

^a Monte Carlo standard errors of Bias, EmpSE and MSE are $\text{EmpSE}/\sqrt{1/10,000}$; $\text{EmpSE}/(2\sqrt{9,999})$;

$\sqrt{\frac{\sum_{i=1}^{10,000} [(\hat{\beta}_i - 6.9)^2 - \text{MSE}]^2}{9,999 \times 10,000}}$, respectively [25].

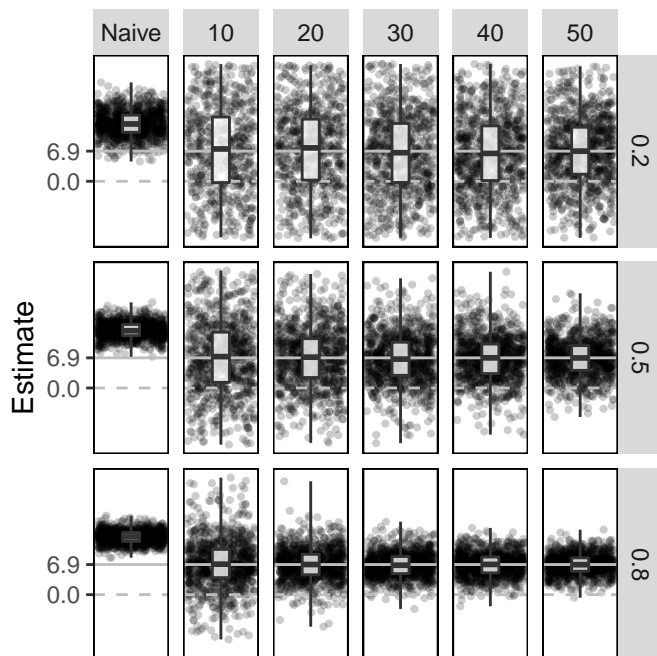


Figure 2.4: Estimates of the treatment effect using the naive estimator and corrected estimator for different values of R-squared (row grids) and different sample sizes of the external validation set (column grids) under differential measurement error ($\theta_{00} = 0$, $\theta_{10} = 1$, $\theta_{01} = 0$, $\theta_{11} = 1.05$). Each grid is based on every 10th estimate of a simulation of 10,000 replicates, using an estimand of 6.9 (indicated by the solid supplementary material line), based on example trial 1 by Makrides et al. [15].

Table 2.5: Coverage and average confidence interval (CI) width of the corrected estimator for differential measurement error ($\theta_0 = 0, \theta_{10} = 1, \theta_{11} = 0, \theta_{12} = 1.05$), R-squared equal to 0.8, 0.5 and 0.2 and different sample sizes of the validation data set. Each scenario is based on 10,000 replicates, the value of the estimand is 6.9, based on example trial 1 by Makridas et al. [15]

Performance Measure ^a	$R^2_{Y,X}$	Naive Estimator ^b	Method for Construction of CI	Corrected Estimator				
				10	20	30	40	50
Coverage (%)	0.8	0.7	Zero-Variance	43.8	59.9	67.9	72.7	76.8
			Delta	97.1	96.6	96.0	95.7	95.9
			Bootstrap	97.9	95.7	94.7	94.5	95.0
0.5	6.7	Zero-Variance	Delta	30.3	43.3	50.2	55.5	61.0
			Delta	97.6	97.6	97.3	96.9	97.0
			Bootstrap	98.4	98.0	96.6	95.8	95.5
0.2	41.1	Zero-Variance	Delta	25.7	35.0	41.9	46.6	52.2
			Delta	98.4	99.0	98.9	98.9	98.9
			Bootstrap	99.0	99.6	99.2	99.0	98.7
Average CI width	0.8	5.7	Zero-Variance	8.2	5.9	5.7	5.7	5.6
			Delta	2688.7	18.3	12.1	10.5	9.5
			Bootstrap	142.6	24.3	13.1	10.7	9.5
0.5	7.2	Zero-Variance	Delta	33.0	17.9	30.3	10.6	7.5
			Delta	463 975.1	49 493.3	660 587.5	13 238.0	18.5
			Bootstrap	303.5	118.8	58.4	34.2	24.0
0.2	11.4	Zero-Variance	Delta	64.6	150.5	53.1	43.1	26.8
			Delta	1 219 162.5	26 998 502.1	486 295.4	85 139.8	3407.5
			Bootstrap	562.9	353.8	283.3	221.4	170.2

^a Monte Carlo standard errors of Coverage are $\sqrt{[Cover \times (1 - Cover)]/10,000}$ [25]

^b Coverage of the true intervention effect using regular Wald CIs of the naive effect estimator.

2.5.4. Measurement error dependent on a prognostic factor

Above, we focused on measurement error in endpoints that are either systematic (linearly dependent on true endpoint) or differential (linearly dependent on true endpoint and exposure). Yet, measurement error could depend on prognostic factors. For example, measurement error in haemoglobin levels measured in capillary blood may differ for women and men [17]. Moreover, haemoglobin levels are, on average, higher in men than in women. To illustrate the effect of measurement error that is dependent on a prognostic factor, we use example trial 1, here assuming that it was conducted in women and men. Data were generated for a sample of $N = 400$ individuals, equally divided in two treatment arms and with equal sex distribution in both arms. Let the proportion of women in the sample be 75% ($S = 1$ for men and $S = 0$ for women). Further, assume $Y = 120 + 6.9X + 10S + \varepsilon$, where ε has mean 0 and $\text{Var}(\varepsilon) = 158.8$. Additionally, assume additive systematic measurement error in Y^* , $Y^* = Y + 0.5S + e$ (additive systematic measurement error in men and random measurement error in women), where e has mean 0 and $\text{Var}(e) = 6.6$ and e independent of Y , X , S and ε . In a simulation of 10,000 replicates we estimated the effect of Y^* on X (naive analysis) and the effect of Y^* on X , conditional for S (conditional analysis). In section S2.4 of the supplementary material, we proof that both analyses will result in correct estimation of the treatment effect. The results of the simulation study show that the average treatment effect estimate of both analyses was 6.89, indicating that there is no bias in either of the analyses. Yet, the empirical variance of the effect estimate in the 10,000 replicates was somewhat lower for the conditional analysis compared to the naive analysis (2.01 vs. 2.22), indicating an efficiency gain in favour of the conditional analysis. By assuming that randomisation was well-performed, measurement error dependent on a prognostic factor does not introduce bias in the naive analysis other than the biases already discussed.

2.6. Discussion

This chapter outlined the ramifications for randomised trial inferences when a continuous endpoint is measured with error. Our study showed that when this measurement error is ignored, not only can trial results be hampered by a loss in precision of the treatment effect estimate (i.e., increased Type-II error for a given sample size), but trial inferences can be impacted through bias in the treatment effect estimator and a null-hypothesis significance test for the treatment effect can deviate substantially from the nominal level. In this chapter we proposed a number of regression calibration-like correction methods to reduce the bias in the treatment effect estimator and obtain CIs with nominal coverage. In our simulation studies, these methods were effective in improving trial inferences when an external validation dataset (containing information about error-prone and error-free measurements) with at least 15 subjects was available.

To anticipate the impact of measurement error on trial inferences, knowledge is needed on the mechanism and magnitude of the measurement error. Endpoints that are measured with purely homoscedastic classical measurement error are expected to reduce the precision of treatment effect estimates and increase Type-II error at a given sample size, proportional to the relative amount of variance that is due to the error. Heteroscedastic classical error and differential error also affect Type-I error. Under systematic measurement error, only Type-I errors for testing null effects are expected to be at the nominal level. The treatment

effect estimator itself is biased by systematic error and differential error. Heteroscedastic error can be addressed using standard robust standard error estimators (e.g., HC3 [19]). Systematic error and differential error in the endpoint can be addressed via regression calibration-like correction methods.

2

We considered regression calibration-like correction methods that rely on an external validation set that contains information about both error-prone and error-free measurements. We anticipate such an external validation set can be feasible as a planned pilot study phase of a trial. Our simulation study shows that the effectiveness of correction methods to adjust the trial results for endpoint measurement error are dependent on the size of the validation sample and the strength of the correlation between the error-free and error-prone measurement of the trial endpoint. For a weak relation ($R^2 = 0.20$) we found the correction methods to be generally ineffective in improving trial inference with reasonably sized validation sets (i.e., up to size $N = 50$). However, for medium ($R^2 = 0.50$) or strong ($R^2 = 0.80$) correlations, the regression calibration showed improvements with external validation samples as small as 15 observations. With the relatively small validation samples (up to 50 observations), our study showed that the bootstrap performed best in constructing CIs in terms of coverage. The use of percentiles might explain that CIs were slightly conservative (i.e., too broad) for small validation samples (10 observations), which may be improved by using bias-corrected and accelerated bootstrap intervals [26]. The proposed regression calibration-like correction methods rely on a linear regression framework and can thus easily be extended to incorporate covariables in the trial analysis [27].

The use of measurement error corrections is still rare in applied biomedical studies with measurement error problems usually reported as an afterthought [9, 14]. Indeed, to our knowledge, no measurement error correction methods have been used so far in the analysis of biomedical trials to correct for measurement error in the endpoint. This may in part be due to a common misconception that measurement error can only affect trial inference by reducing the precision of estimating the effect of treatment and increasing Type-II error, which can be improved by increasing the study sample size. Note that our study demonstrates that such an assumption is warranted only when strict classical homoscedastic error structure of the trial endpoint can be assumed. Such does not hold, for instance, when measurement error are more pronounced in the tails of the distribution, or when measurement error vary between treatment arms.

Instead of the use of external validation datasets, internal measurement correction approaches where both the preferred endpoint and the error contaminated endpoint are measured on a subset of trial participants may sometimes be more feasible. For internal validation, Keogh et al. [7] recently reviewed methods of moment estimation and maximum likelihood estimation approaches. There are also other approaches to correct for measurement error that we did not discuss in this chapter. For instance, Cole and colleagues suggested a multiple imputing approach based on an internal validation set [28]. We also only focused on continuous outcomes in this chapter. Problems and solutions for misclassified categorical outcomes can be found elsewhere [29]. Yet, to the best of our knowledge, none of these methods have been tested in the setting where trial endpoints are measured with error and thus need further study.

Lastly, we solely discuss parametric measurement error models, which might misspecify the measurement error model. The extent to which the distribution of the unmeasured outcome can be estimated without parametric assumptions is a question for further

research. In the context of measurement error in explanatory variables this is formerly described as deconvolution ([10], Chapter 12 and references therein). Further, the method of non-parametric maximum likelihood has been successfully applied for explanatory variables measured with error [30, 31] and this might be an avenue of future research.

In summary, the impact of measurement error in a continuous endpoint on trial inferences can be particularly non-ignorable when the measurement error is not strictly random, because Type-I error, Type-II and the effect estimates can be affected. To alleviate the detrimental effects of measurement error we proposed measurement error corrected estimators and a variety of methods to construct CIs for non-random measurement error. To facilitate the implementation of these measurement error correction estimators we have developed the R package *mecor*, available at: <https://github.com/LindaNab/mecor>.

References

- [1] E. Cerin, K. Cain, A. Oyeyemi, N. Owen, T. Conway, T. Cochrane, D. Van Dyck, J. Schipperijn, J. Mitáš, M. Toftager, I. Aguinaga-Ontoso, J. Sallis, Correlates of agreement between accelerometry and self-reported physical activity, *Medicine & Science in Sports & Exercise* 48 (6) (2016) 1075–1084. doi:10.1249/MSS.0000000000000870.
- [2] M. Lauer, R. D'Agostino, The randomized registry trial: The next disruptive technology in clinical research?, *New England Journal of Medicine* 369 (17) (2013) 1579–1581. doi:10.1056/NEJMp1310102.
- [3] I. Boutron, F. Tubach, B. Giraudeau, P. Ravaud, Blinding was judged more difficult to achieve and maintain in nonpharmacologic than pharmacologic trials, *Journal of Clinical Epidemiology* 57 (2004) 543–550. doi:10.1016/j.jclinepi.2003.12.010.
- [4] H. Staudacher, P. Irving, M. Lomer, K. Whelan, The challenges of control groups, placebos and blinding in clinical trials of dietary interventions, *Proceedings of the Nutrition Society* 76 (2017) 203–112. doi:10.1017/S0029665117000350.
- [5] S. Mahabir, D. Baer, C. Giffen, A. Subar, W. Campbell, T. Hartman, B. Clevidence, D. Albanes, P. Taylor, Calorie intake misreporting by diet record and food frequency questionnaire compared to doubly labeled water among postmenopausal women., *European Journal of Clinical Nutrition* 60 (2006) 561–565. doi:10.1038/sj.ejcn.1602359.
- [6] S. Senn, S. Julious, Measurement in clinical trials: A neglected issue for statisticians?, *Statistics in Medicine* 28 (2009) 3189–3209. doi:10.1002/sim.3603.
- [7] R. H. Keogh, R. J. Carroll, J. A. Tooze, S. I. Kirkpatrick, L. S. Freedman, Statistical issues related to dietary intake as the response variable in intervention trials, *Statistics in Medicine* 35 (25) (2016) 4493–4508. doi:10.1002/sim.7011.
- [8] J. Buonaccorsi, *Measurement error: Models, methods, and applications*, Chapman & Hall/CRC, Boca Raton, FL, 2010.
- [9] T. B. Brakenhoff, M. Mitroiu, R. H. Keogh, K. G. M. Moons, R. H. H. Groenwold, M. van Smeden, Measurement error is often neglected in medical literature: A systematic review, *Journal of Clinical Epidemiology* 98 (2018) 89–97. doi:10.1016/j.jclinepi.2018.02.023.
- [10] R. Carroll, D. Ruppert, L. Stefanski, C. Crainiceanu, *Measurement error in nonlinear models: A modern perspective*, 2nd Edition, Chapman & Hall/CRC, Boca Raton, FL, 2006.
- [11] W. Fuller, *Measurement error models*, John Wiley & Sons, New York, NY, 1987.
- [12] P. Gustafson, *Measurement error and misclassification in statistics and epidemiology: Impacts and Bayesian adjustments*, Chapman & Hall/CRC, Boca Raton, FL, 2004.
- [13] J. A. Hutcheon, A. Chiolero, J. A. Hanley, Random measurement error and regression dilution bias, *BMJ* 340 (c2289) (2010). doi:10.1136/bmj.c2289.

- [14] P. A. Shaw, V. Deffner, R. H. Keogh, J. A. Tooze, K. W. Dodd, H. Küchenhoff, V. Kipnis, L. S. Freedman, Epidemiologic analyses with error-prone exposures: Review of current practice and recommendations, *Annals of Epidemiology* 28 (11) (2018) 821–828. doi:10.1016/j.annepidem.2018.09.001.
- [15] M. Makrides, C. Crowther, R. Gibson, R. Gibson, C. Skeaff, Efficacy and tolerability of low-dose iron supplements during pregnancy: A randomized controlled trial, *American Journal of Clinical Nutrition* 78 (1) (2003) 145–153. doi:10.1093/ajcn/78.1.145.
- [16] S. Zlotkin, P. Arthur, K. Antwi, G. Yeung, Randomized, controlled trial of single versus 3-times-daily ferrous sulfate drops for treatment of anemia, *Pediatrics* 108 (3) (2001) 613–616. doi:10.1542/peds.108.3.613.
- [17] A. Patel, R. Wesley, S. Leitman, B. Bryant, Capillary versus venous haemoglobin determination in the assessment of healthy blood donors, *Vox Sanguinis* 104 (4) (2013) 317–323. doi:10.1111/vox.12006.
- [18] R. H. Keogh, I. R. White, A toolkit for measurement error correction, with a focus on nutritional epidemiology, *Statistics in Medicine* 33 (12) (2014) 2137–2155. doi:10.1002/sim.6095.
- [19] J. S. Long, L. H. Ervin, Using heteroscedasticity consistent standard errors in the linear regression model, *The American Statistician* 54 (3) (2000) 217–224. doi:10.2307/2685594.
- [20] G. Fitzmaurice, Measurement error and reliability, *Nutrition* 18 (1) (2002) 112–114. doi:10.1016/s0899-9007(01)00624-4.
- [21] J. Buonaccorsi, Measurement errors, linear calibration and inferences for means, *Computational Statistics & Data Analysis* 11 (3) (1991) 239–257. doi:10.1016/0167-9473(91)90083-E.
- [22] B. Efron, Bootstrap methods: Another look at the jackknife, *Annals of Statistics* 7 (1) (1979) 1–26. doi:10.1214/aos/1176344552.
- [23] L. S. Freedman, D. Midthune, L. Arab, R. L. Prentice, A. F. Subar, W. Willett, M. L. Neuhauser, L. F. Tinker, V. Kipnis, Combining a food frequency questionnaire with 24-hour recalls to increase the precision of estimation of usual dietary intakes—Evidence from the validation studies pooling project, *American Journal of Epidemiology* 187 (10) (2018) 2227–2232. doi:10.1093/aje/kwy126.
- [24] A. Burton, D. Altman, P. Royston, R. Holder, The design of simulation studies in medical statistics, *Statistics in Medicine* 25 (24) (2006) 4279–4292. doi:10.1002/sim.2673.
- [25] T. P. Morris, I. R. White, M. J. Crowther, Using simulation studies to evaluate statistical methods, *Statistics in Medicine* 38 (11) (2019) 2074–2102. doi:10.1002/sim.8086.
- [26] P. Hall, Rejoinder: Theoretical comparison of bootstrap confidence intervals, *The Annals of Statistics* 16 (3) (1988) 981–985. doi:10.1214/aos/1176350944.

- [27] S. Senn, Covariate imbalance and random allocation in clinical trials, *Statistics in Medicine* 8 (1989) 467–475. doi:10.1002/sim.4780080410.
- [28] S. R. Cole, H. Chu, S. Greenland, Multiple-imputation for measurement-error correction, *International Journal of Epidemiology* 35 (4) (2006) 1074–1081. doi:10.1093/ije/dyl097.
- [29] D. Brooks, K. Getz, A. Brennan, A. Pollack, M. Fox, The impact of joint misclassification of exposures and outcomes on the results of epidemiologic research, *Current Epidemiology Reports* 5 (2) (2018) 166–174. doi:10.1007/s40471-018-0147-y.
- [30] S. Rabe-Hesketh, A. Pickles, A. Skrondal, Correcting for covariate measurement error in logistic regression using nonparametric maximum likelihood estimation, *Statistical Modelling* 3 (3) (2003) 215–232. doi:10.1191/1471082X03st056oa.
- [31] S. Rabe-Hesketh, A. Skrondal, A. Pickles, Maximum likelihood estimation of generalized linear models with covariate measurement error, *The Stata Journal: Promoting communications on statistics and Stata* 3 (4) (2003) 386–411. doi:10.1177/1536867X0400300408.