Treatments comparison in longitudinal clinical trials with informative dropouts

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Abstract

The main objective of longitudinal clinical trials is to compare the treatment effects depending on an outcome variable. Standard techniques can be used when all intended measurements for all subjects are available. Some patients may leave the study prematurely resulting in monotone missing data (dropout). A major problem arises when the probability of dropout is related to the outcome variable, this often reffered to as informative or non-ignorable dropout. Ignoring the missing data in this case leads to biased estimates of treatment effect differences. This paper proposes and developes the stochastic EM algorithm to obtain valid estimates of treatment comparisons. The proposed algorithm is a variant of imputation approaches, which are conceptually and practically simple and are commonly used by practitioners. Simulation studies are conducted to evaluate the proposed approach and to compare it with three common approaches; the "last value carrying forward" (LVCF) approach, the "all available data" (AAD) approach and the "partial imputation approach" (PI). Simulation results show that the stochastic EM approach provides unbiased treatment comparisons, or at least "less" biased, comparable to the other three approaches. The stochastic EM approach, also, can be used to estimate individual treatment effects, not only comparing treatment effects, as the case with other approaches.

1 INTRODUCTION

clinical trials are, sometimes, designed to take repeated measurements of an outcome variable at several predefined times after randomization for all individuals in the study. Typically, in a longitudinal clinical trial the study objective is to estimate and compare two or more treatement effects and to select the one that is most effective in dealing with some disease or disorder. Missing values are not uncommon in longitudinal clinical trials because some patients may dropout of the

study all together (dropout pattern), or they fail to appear for some of the scheduled visits (intermittent pattern), due to several reasons. Some of these reasons are, for example, recovery, lack of improvement, or removal from the study due to adverse events (Heyting *et al.*, 1992). Analysing longitudinal clinical trials data in the precense of missing values tend to be more complicated. Removing dropouts from the analysis can produce serious bias in the assessment of treatment effects especially if the number of subjects with missing values is large comparable with the total number of subjects. Hence, procedures for handling dropouts need to be developed and considered. Some of these techniques are described in Gornbein (1992) and Murray (1998). Also a recent review of these methods is in Fitzmaurice (2003) and references therein.

Assume that Y_{kij} is the response variable for the ith subject in the treatment group k, $k = 1, 2, ..., G$, at time t_j, $(j = 1, 2, ..., n)$. Also, assume that there are m_k subjects in the treatment group k. Any subject, in any treatment group, with complete observations has an $n \times 1$ vector of measurements, $Y_{ki} = (Y_{ki1}, ..., Y_{kin})$. Let μ_{kj} denote the mean of intended measurements of all subjects in treatment k at time point t_j. Let D_{ki} denote the dropout variable, if $D_{ki} < t_n$ the ith subject in group k is a dropout, otherwise, a study completer. The dropout variable, D_{ki} may be a function of subject's follow-up time. It is common to assume that the dropout time is discrete, hence $t_1, t_2, ..., t_n$ are the set of ordered dropout times, with $D_{ki} = t_n$ for the study completers. Assume that the complete set of responses for subject i at treatment k, Y_{ki}, is partitioned into $Y_{ki,obs}$ and $Y_{ki,mis}$ where $Y_{ki,obs}$ are the observed measurements for the ith subject in group k and $Y_{ki,mis}$ are the missing responses.

The joint probability density function of Y_{ki} and D_{ki}, $f(Y_{ki}, D_{ki})$, can be factorised as:

$$f(Y_{ki}, D_{ki}) = f(Y_{ki}) P(D_{ki}|Y_{ki}),$$

where the distribution functions are implicity indexed by its associated parameters. This factorisation is known as selection model in the literature. Rubin (1976) has introduced a very usefull taxonomy of missing data process. Following Rubin's taxonomy, in the context of a longitudinal clinical trial with dropouts, three types of dropout mechanisms can be defined; See for example Laird (1988) and Diggle and Kenward (1994). The first is a missing completely at random (MCAR) mechanism, where the dropout is assumed to be independent of both $Y_{ki,obs}$ and $Y_{ki,mis}$. That is:

$$P(D_{ki}|Y_{ki}) = P(D_{ki}).$$

The second type of dropout mechanisms is a missing at random (MAR), where the dropout is conditionally independent of $Y_{ki,mis}$ given $Y_{ki,obs}$, that is:

$$P(D_i|Y_{i,obs}, Y_{i,mis}) = P(D_i|Y_{i,obs}).$$

The third type of dropout mechanisms is an informative (non-ignorable) dropout mechanism, where dropout depends on the missing responses and may be on the

observed measurements. Another factorisation of the joint distribution of Y_{ki} and D_{ki}, $f(Y_{ki}, D_{ki})$, known as pattern mixture model, as:

$$f(Y_{ki}, D_{ki}) = f(Y_{ki}|D_{ki})P(D_{ki}).$$

The parameters of the conditional distribution $f(Y_{ki}|D_{ki})$ or either the marginal distribution $f(Y_{ki})$ can be used to compare treatment groups. Comparing the treatment groups using the parameters of the marginal distribution $f(Y_{ki})$ has been studied by, for example, Heyting *et al.* (1992), Glidden and Wei (1997), Rotnitzky and Robins (1995), Troxel *et al.* (1997), Wei and Shih (2001), Wu and Carroll (1988) and Yao *et al.* (1998).

Several methods have been proposed in the literature to handle the problem of dropout to yield valid analyses. A recent review of methods for handling dropouts in longitudinal clinical trials has been presented by Fitzmaurice (2003). The first method is the complete case analysis (CCA) where subjects with only complete observations are included in the analysis. This method yields biased treatment comparisons except under the unrealastic assumption that the missing data process is missing completely at random, MCAR. In other words this type of analysis assumes that the completers are random sample of subjects.

In the second method, the all available data (AAD) approach, the analysis is based on all available observations for all subjects. Again this approach needs the MCAR assumption but it is more efficient than the CCA, where the partial information available on subjects with missing data may improve the parameter estimates.

The third method is the imputation approach where the missing values are imputed by chosen values and the pseudo complete observations are analysed. The imputation approach is a very general term and many methods can be veiwed as imputation methods ranging from simple imputation methods to the methods that need very sophesticated models. The multiple imputation method is a variant of these methods (Rubin, 1987). Another variant is the "last value carried forward" (LVCF) method which is a common method for analysing longitudinal clinical trials among practitioners. This method is based on a very unrealastic assumption that the responses following the dropout remain constant. Recently, Wei and Shih (2001) propose another variant of imputation methods, the partial imputation approach (PI), for handling informative dropout. In the PI approach, the missing values are partially imputed by carrying forward the last observed value, so that the dropout rates are similar for the two treatments. This approach performs well comparable to the AAD, the LVCF, and the mixed effects approaches. This approach assumes that the last observed value remains constant and can be used only for treatment comparisons. The PI approach still give biased treatment differences when there are different correlations between the dropout process and the response variable in both treatments.

Gad and Kenward (2002) use the stochastic EM algorithm to obtain parameter estimates in the longitudinal data context. They assume that the response variable

follows a skew distribution whereas in the current paper the response variable is normally distributed. In Gad and Kenward (2002) the dropout process is modelled using logistic regression which is not the case in this paper.

The aim of this paper is to introduce the stochastic EM algorithm as a way of estimating the treatment differences. The treatments is compared using the parameters of the marginal distribution, $f(Y_{kl})$. The stochastic EM algorithm is a variant of imputation methods, which are commonly used by practitioners. This approach can overcome the drawbacks of the forementioned methods. It provides unbiased, or at least less biased, estimates of treatment differences in the presence of informative dropout regardless of the correlation type between the dropout variable and the responses. In addition to treatment comparisons, the stochastic EM algorithm can be used to estimate the individual treatment effects. In the following section the main principles of the stochastic EM algorithm are presented. In Section 3 simulation studies are conducted to evaluate the proposed algorithm and to compare it with the LVCF approach, the AAD approach, and the PI approach. Finally, in Section 4, conclusion and discussion are presented.

2 THE STOCHASTIC EM ALGORITHM

The E-step of the EM algorithm becomes untractable and not easy to execute in some situations. The stochastic EM algorithm has been introduced as an alternative algorithm by Celeux and Diebolt (1985). In the stochastic EM algorithm, the E-step of the EM algorithm, is replaced by simulation step (S-step) to overcome the difficulties of finding the appropriate expectations. The stochastic EM algorithm involves iterating two steps: the S-step and the maximization step (M-step). At the S-step, the missing values are simulated from the conditional distribution of the missing values given the observed values and the current parameter estimates. The simulated values in addition to the observed values constitiute pseudo complete data. At the M-step, the parameter estimates are obtained based on the pseudo complete data. The entire procedure is iterated for sufficient number of iterations. The parameter estimates corresponding to each pseudo complete data form a Markov chain of estimates, $\{\theta^{(t)}\}$. Ip (1994) proves, under specific conditions, that this Markov chain $\{\theta^{(t)}\}$ generated by the stochastic EM algorithm is ergodic. Moreover it generally converges reasonably fast to its stationary distribution, which is unique (Diebolt and Ip, 1996).

In the stochastic EM algorithm a sequence of parameters estimates are obtained instead of a single point estimate. An important issue is how to use this sequence to find a point estimate for the underlying parameters. It is possible to find two point estimates using the sequence of estimates generated by the stochastic EM algorithm. Although generally the exact stationary distribution $\pi(.)$ is not known, it can be approximated by its empirical version. The mean of the stationary distribution $\pi(.)$ can be considered as an estimate for the parameters θ. This

estimate is called the stochastic EM estimate and is denoted by $\tilde{\theta}$ (Diebolt and Ip, 1996). The first early s_0 iterations, the burn-in period, are discarded to avoid the influence of the starting points. Thus, this estimate can be obtained as:

$$\tilde{\theta} = 1/(s - s_0) \sum_{j=s_0+1}^{s} \theta^{(j)},$$

where s is the total number of iterations. The integers s and s_0 should be chosen large enough to ensure that the Markov chain $\{\theta^{(t)}\}$ is close to its stationary distribution. In general, this estimate does not agree with the maximum likelihood estimates (MLE's). For example, in the exponential family distributions, $\tilde{\theta}$ differs from MLE's by a magnitude of $O(1/n)$ (see Diebolt and Ip (1996) for details). In some simple examples $\tilde{\theta}$ coincides with the MLE's. Throughout this paper $\tilde{\theta}$ is considered to be the stochastic EM estimate. The second point estimate that can be considered is the point with the largest log-likelihood value over the chain. This point is reasonably close to the maximum likelihood estimate for most practical purposes (Diebolt and Ip, 1996). However, obtaining this point needs an extra effort for evaluating the log-likelihood function at each iteration.

It is obvious that convergence of the resulting sequence of parameter estimates from the stochastic EM algorithm needs to be monitored. Monitoring convergence of such chains can be done visually or using a formal method. Several methods have been described in the literature for this purpose, see for example, Brooks and Roberts (1998), Cowles and Carlin (1996) and Mengersen *et al.* (1999). In this paper the method which has been introduced by Gelman and Rubin (1992) is suggested to monitor convergence of the chains. This method is based on generating multiple, $r \geq 2$, parallel chains for $q = 2p$ iterations. For each chain this method sugests starting from different initial points for which the starting distribution is over-dispersed compared to the target distribution. This method is seperately monitoring the convergence of each scalar parameter of interest from the target distribution by evaluating the scale reduction factor $\sqrt{\hat{R}}$ as

$$\sqrt{\hat{R}} = \sqrt{(p-1)/p + B/pW},$$

where W is the mean of within sequence variances and B/p is the between sequences varaince. These calculations depends on the last p iterations of each sequence. The convergence is achieved if the scale reduction factor is close to 1 which means that the parallel Markov chains are essentially overlapping. If the scale reduction factor is high, then proceeding with further simulations may improve the inference.

In longitudinal clinical trials assuming that there are two treatment groups $k = 1, 2$, hence $Y_{1i} = (Y_{1i,obs}, Y_{1i,mis})$ is the response variable of subject i in the first treatment group, where $Y_{1i,obs}$ and $Y_{1i,mis}$ are the observed and the missing components respectively. Also, $Y_{2i} = (Y_{2i,obs}, Y_{2i,mis})$ is the response variable of

the ith subject in group 2. The aim is to estimate the treatment differences $\mu_{dj} = \mu_{2j} - \mu_{1j}$ at the different time points. The steps of the stochastic EM algorithm are as follows:

- **S-Step:** At the (t+1)th iteration, the missing data $Y_{1i,mis}$ and $Y_{2i,mis}$ are simulated from the conditional density functions $f(Y_{1i,mis}|Y_{1i,obs}, D_1, \theta^{(t)})$ and $f(Y_{2i,mis}|Y_{2i,obs}, D_2, \theta^{(t)})$ respectively, where $\theta^{(t)}$ is the current parameter estimate of θ. This imputation of $Y_{i,mis}$ is based on all current information about θ, and hence provides us with plausible set of pseudo complete data. The parameters θ are the relevant components of the mean vectors and covariance matrices. When the conditional distributions have standard forms this simualtion step can be easily implemented using any standard statistical package. Otherwise, Markov chain Monte carlo methods can be used.

- M-Step: Having the pseudo complete data, parameter estimates can be obtained using standard procedures to update the parameter estimates, $\theta^{(t+1)}$. In this step the treatment differences $\mu_{dj}^{(t)}$, $j = 1, ..., n$ are obtained. The two steps are iterated for sufficient number of iterations, s.

The stochastic EM estimate of the vector μ_{dj} can be obtained as:

$$\tilde{\mu}_{dj} = 1/(s - s_0) \sum_{j=s_0+1}^{s} \mu_{dj}^{(j)}.$$

3 SIMULATION STUDIES

Three simulations are presented in this section with three different configurations. These configurations are the same as that used in Wei and Shih (2001). The reason behind that is to be able to compare results from the stochastic EM approach with the previous approaches. The stochastic EM approach is used to estimate treatments difference in addition to three other approaches; the LVCF, the AAD, and the PI approaches. For the stochastic EM algorithm the iterations number (s) is set to 5000 and the burn-in period (s_0) equals to 1000. The Gelman-Rubin method is used to check the convergence of the stochastic EM chains. The necessary codes for conducting the three simulation studies are written using MATLAB package version 5.2. The codes are available from the author on request.

3.1 Simulation 1: MCAR situation

Assume that there are 4 intended measurements for each subject in each treatment group at time-points $t = 12, 20, 32$ and 48 weeks after randomisation. Assume also there are two treatment groups, $k = 1, 2$. Let $Y_{ki} = (Y_{ki1}, Y_{ki2}, Y_{ki3}, Y_{ki4})$ be the response of subject i in treatment k at the specified time points. Also, let D_k be

the log follow-up time for treatmment group k ($k = 1, 2$). Let the random vector Y_{ki}^* be the response of subject i in treatment k augmented by the dropout variable for that treatment group D_k, hence, $Y_{ki}^* = (Y_{ki1}, Y_{ki2}, Y_{ki3}, Y_{ki4}, D_k)$. Assuming that each treatment group has 150 subjects, so 150 samples of each of the random vectors Y_{1i}^* and Y_{2i}^* are simulated from multivariate normal distributions with mean vectors $\mu_{1j} = (400, 395, 390, 385, 4.6)$ and $\mu_{2j} = (425, 435, 445, 455, 5.0)$ and with the same correlation/covariance matrix Σ (correlation in the upper and covariance in the lower off-diagonal elements), where

$$\Sigma = \begin{pmatrix} 2560 & 0.60 & 0.40 & 0.38 & 0 \\ 1530 & 2560 & 0.60 & 0.40 & 0 \\ 1026 & 1530 & 2560 & 0.60 & 0 \\ 980 & 1026 & 1530 & 2560 & 0 \\ 0 & 0 & 0 & 0 & 2 \end{pmatrix}.$$

The true treatment differences are $\mu_{dj} = (25, 40, 55, 70)$. For each subject in each treatment group the dropout time is determined by comparing D_k and the time points. The simulation process is repeated 1000 times, i.e. there are 1000 data sets each has 150 subjects in each treatment group k, $k = 1, 2$. This is an MCAR situation because the dropout variable is independent of the response variable. The dropout variables D_1 and D_2 have different means but the same variance.

The stochastic EM algorithm is applied to estimate the treatment differences. In the S-step the missing values, $Y_{ki,mis}$, are generated from multivariate normal distribution with the appropriate mean vector and covariance matrix. It appears, using the Gelman-Rubin method, that the resulting chains converge well. Also the LVCF, the AAD and the PI approaches are applied to estimate the treatment differences and the results are given in Table 1.

The LVCF approach underestimate the true parameter values especially at the last two time points where the dropout rate is high and the dropout distributions are different. Also, the 95% confidence interval coverage is far from the nominal level especially in the last time point. The parameter estimates using the AAD approach, the PI approach and the stochastic EM approach are empirically unbiased. The confidence interval coverage are close to the nominal level using the three approaches.

3.2 Simulation 2: informative dropout situation

In this simulation the response vectors in the first group are simulated from multivariate normal distributions with mean (400, 395, 390, 385, 4.4) and with the co-

Table 1: Simulation 1: treatment effects = $(25, 40, 55, 70)$ at weeks $12, 20, 32$ and 48 respectively

	Dropout rate %	AAD		LVCF			PI		stochastic EM	
	G1/G2	Est. (SE)	Coverage of 95 % CI	Est. (SE)	Coverage of 95 % CI	Dropout rate after partial imputation %	Est. (SE)	Coverage of 95 % CI	Est. (SE)	Coverage of 95 % CI
Week 12	6.8/3.8	24.9 (6.0)	0.948	24.9 (6.0)	0.948	6.8/3.8	24.9 (6.0)	0.948	24.9 (5.9)	0.944
Week 20	12.9/7.9	40.1 (6.2)	0.955	39.2 (6.0)	0.949	8.5/7.9	39.8 (6.1)	0.951	39.9 (5.9)	0.955
Week 32	21.2/13.9	55.3 (6.4)	0.957	52.5 (6.0)	0.930	13.9/13.9	54.8 (6.3)	0.959	55.1 (6.1)	0.945
Week 48	30.4/21.3	70.3 (6.8)	0.942	64.4 (6.0)	0.844	21.2/21.3	69.6 (6.6)	0.955	70.1 (6.1)	0.939

variance/correlation matrix Σ_1, where

$$\Sigma_1 = \begin{pmatrix} 2560 & 0.60 & 0.40 & 0.38 & 0.75 \\ 1530 & 2560 & 0.60 & 0.40 & 0.75 \\ 1026 & 1530 & 2560 & 0.60 & 0.75 \\ 980 & 1026 & 1530 & 2560 & 0.75 \\ 54 & 54 & 54 & 54 & 2 \end{pmatrix}.$$

In the second treatment group the mean vector is $(425, 435, 445, 455, 7.4)$ and the covariance/correlation matrix Σ_2, where

$$\Sigma_2 = \begin{pmatrix} 2560 & 0.60 & 0.40 & 0.38 & 0.75 \\ 1530 & 2560 & 0.60 & 0.40 & 0.75 \\ 1026 & 1530 & 2560 & 0.60 & 0.75 \\ 980 & 1026 & 1530 & 2560 & 0.75 \\ 142 & 142 & 142 & 142 & 14 \end{pmatrix}.$$

In this situation the dropout variable is related to the response variable hence the dropout process is informative. Note that the dropout variable has equal correlations with the response variable in both treatment groups but with different mean and variance. From results in Table 2, it is noticed that the dropout rate in the first treatment group is higher than the second treatment group except in the week 12. The AAD analysis seriously underestimates the treatment difference especially in the last time point and the empirical coverage of the 95% confidence interval is far away from the nominal level. The AAD approach is less biased than the LVCF approach but still underestimate the treatment effects. The empirical coverage of 95% confidence interval is far from the nominal level in the last time point. The PI approach gives almost unbiased treatment effects and a reasonable coverage of 95% confidence interval. The stochastic EM approach provides unbiased treatment effects and the empirical coverage of 95% confidence intervals is closer to the nominal level. It can be concluded that, in this situation, the stochastic EM algorithm performs well and it is superior to the other three approaches.

3.3 Simulation 3: informative dropout situation

In this simulation the same configuration is used as in the second simulation but Σ_2 is defined as:

$$\Sigma_2 = \begin{pmatrix} 2560 & 0.60 & 0.40 & 0.38 & 0.51 \\ 1530 & 2560 & 0.60 & 0.40 & 0.51 \\ 1026 & 1530 & 2560 & 0.60 & 0.51 \\ 980 & 1026 & 1530 & 2560 & 0.51 \\ 96 & 96 & 96 & 96 & 14 \end{pmatrix}.$$

Table 2: Simulation 1: treatment effects = (25, 40, 55, 70) at weeks 12, 20, 32 and 48 respectively

	Dropout rate %	AAD		LVCF			PI		stochastic EM	
	G1/G2	Est. (SE)	Coverage of 95 % CI	Est. (SE)	Coverage of 95 % CI	Dropout rate after partial imputation %	Est. (SE)	Coverage of 95 % CI	Est. (SE)	Coverage of 95 % CI
Week 12	8.8/9.4	25.2 (5.6)	0.945	25.2 (5.6)	0.945	8.8/9.4	25.2 (5.6)	0.945	24.9 (5.8)	0.949
Week 20	16.0/12.0	37.3 (5.6)	0.912	39.4 (5.6)	0.941	12.0/12.0	39.6 (5.6)	0.928	39.8 (5.8)	0.936
Week 32	25.4/14.7	48.7 (5.7)	0.798	53.1 (5.6)	0.928	14.8/14.7	54.2 (5.6)	0.933	54.8 (5.8)	0.949
Week 48	35.5/17.3	59.9 (5.9)	0.588	66.0 (5.6)	0.885	17.3/17.3	68.7 (5.6)	0.927	70.3 (5.8)	0.942

This is dependent dropout situation where the dropout variable is correlated to the response variable. This correlation is different for the two treatment groups. The four approaches are used to obtain mean differences for the two treatments and the results are shown in Table 3.

The cumulative dropout rate in the first treatment group is higher than the second treatment group except in the first time point. Again the AAD approach seriously underestimates the treatment effects and the empirical coverage of 95% confidence intervals are very far away from the nominal level. The LVCF approach and the PI approach results are worsen comparable to the previous simulation because the treatment effects are more biased. It can be noticed the the LVCF and the PI approaches are less biased than the AAD approach. The empirical coverage of 95% confidence intervals are far from the nominal level but more reasonable than the AAD approach. On the other hand the stochastic EM approach provides less biased treatment effects. Also the empirical coverage of 95% confidence intervals are very close to the nominal level.

It can be concluded from the above simulations that the stochastic EM approach provides less biased treatment effects when the dropout variable is correlated to the response variable, i.e. the dependent dropout process. This includes whether the dropout variable is equally correlated or not to the response variable. The AAD, the LVCF, and the PI approaches give similar results in MCAR situation. The PI approach improves the biasedness when the dropout process is equally related to the response variable, comparable to the AAD and the LVCF approaches. When the dropout process has different correlation in the two treatment groups, the PI gives biased treatment effects similar to the LVCF approach and AAD, although it is slightly improves the bias. In this situation still the stochastic EM approach provides unbiased treatment effects. In summary, the stochastic EM approach can be considered as an efficient way of estimating and testing the treatment differences in the presence of dependent dropouts regardless of the correlation type between the dropout and the response variable.

4 CONCLUSION AND DISCUSSION

In this paper the stochastic EM algorithm is presented as a way to estimate the treatment differences in longitudinal clinical trials in the presence of informative dropouts. This algorithm is simple and does not need sphosticated models. Under normality assumption the simulation step (S-step) is performed using standard techniques because the conditional distribution is still normal. Because this approach can be viewed as an imputation procedure it is very easy to implement from the practitioners point of veiw.

The stochastic EM approach can be recommended to estimate and test the treatment differences of the response variable. The obtained estimates are unbiased, or at least less biased, and the coverage of confidence intervals are very close

Table 3: Simulation 1: treatment effects = (25, 40, 55, 70) at weeks 12, 20, 32 and 48 respectively

	Dropout rate %	AAD		LVCF			PI		stochastic EM	
	G1/G2	Est. (SE)	Coverage of 95 % CI	Est. (SE)	Coverage of 95 % CI	Dropout rate after partial imputation %	Est. (SE)	Coverage of 95 % CI	Est. (SE)	Coverage of 95 % CI
Week 12	8.7/9.4	22.9 (5.8)	0.932	22.9 (5.8)	0.932	8.7/9.4	22.9 (5.8)	0.932	24.9 (5.9)	0.945
Week 20	16.0/11.9	34.4 (5.8)	0.844	37.1 (5.8)	0.925	11.9/11.9	36.8 (5.8)	0.915	40.2 (5.9)	0.944
Week 32	25.3/14.5	45.4 (5.9)	0.645	51.0 (5.7)	0.898	14.6/14.5	51.0 (5.8)	0.897	55.0 (5.9)	0.943
Week 48	35.2/17.2	56.0 (6.1)	0.370	63.7 (5.8)	0.819	17.2/17.2	64.7 (5.8)	0.847	70.0 (5.8)	0.939

to the nominal levels. This algorithm also can be used to estimate the individual treatment effects in addition to treatment differences. This is an advantage of this approach comparable to other approaches, the PI approach for example. Wei and Shih (2001) pointed out that their approach, the PI approach, can be applied only for treatment difference estimation and testing. Also Wei and Shih (2001) stated that the PI approach gives unbiased treatment differences under the assumption of equal dependece between the dropout process and the response variable in the two treatments. When this assumption is violated the PI approach gives less bias and better empirical confidence coverage than the AAD and the LVCF approahces. In such situation the stochastic EM approach still gives unbiased treatment differences and empirical confidence coverage very close to the nominal level.

In summary the stochastic EM algorithm is an appropriate approach to estimate and test the treatment differences (individual treatment effects), whether the dropout variable is equally correlated to the response variable or not, and the obtained estimates are unbiased or at least less biased.

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