STATISTICS IN MEDICINE
*Statist. Med.* 2009; **28**:572–585
Published online 12 December 2008 in Wiley InterScience
(www.interscience.wiley.com) DOI: 10.1002/sim.3494

# A Bayesian sensitivity model for intention-to-treat analysis on binary outcomes with dropouts

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SUMMARY

Intention-to-treat (ITT) analysis is commonly used in randomized clinical trials. However, the use of ITT analysis presents a challenge: how to deal with subjects who drop out. Here we focus on randomized trials where the primary outcome is a binary endpoint. Several approaches are available for including the dropout subject in the ITT analysis, mainly chosen prior to unblinding the study. These approaches reduce the potential bias due to breaking the randomization code. However, the validity of the results will highly depend on untestable assumptions about the dropout mechanism. Thus, it is important to evaluate the sensitivity of the results across different missing-data mechanisms. We propose here a Bayesian pattern-mixture model for ITT analysis of binary outcomes with dropouts that applies over different types of missing-data mechanisms. We introduce a new parameterization to identify the model, which is then used for sensitivity analysis. The parameterization is defined as the odds ratio of having an endpoint between the subjects who dropped out and those who completed the study. Such parameterization is intuitive and easy to use in sensitivity analysis; it also incorporates most of the available methods as special cases. The model is applied to TRial Of Preventing HYpertension. Copyright © 2008 John Wiley & Sons, Ltd.

KEY WORDS: randomized-controlled trials; binary outcomes; missing data; sensitivity analysis; TROPHY trial

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Contract/grant sponsor: Publishing Arts Research Council; contract/grant number: 98-1846389

*Received 17 March 2008*
*Accepted 14 October 2008*

## 1. INTRODUCTION

Intention-to-treat (ITT) analysis is commonly used when analyzing randomized-controlled trials. Mainly, because it keeps the between-group balance in patients' characteristics achieved by randomization, yields information about the efficacy of treatments when used in practice, and avoids possible bias due to treatment-based differential dropouts rate [1]. The ITT approach requires that all subjects be included in the analysis based on their randomized group regardless of the actual treatment received or subsequent dropout from the study. A complete ITT analysis is thus possible when (1) the subjects are analyzed based on their randomized groups and (2) when fully observed outcome data are available for all randomized subjects. In this article we focus on how to handle missing data in the ITT analysis when the primary outcome is binary, assuming full patient compliance with the assigned treatments. For more discussion in ITT analysis, see Little and Yau [2] and Kleinman *et al.* [3].

In clinical trials with missing outcomes, analysis based only on the observed data will often result in inferences that may well not be valid. As a result, models that account for the missing data are, therefore, increasingly used to adjust for possible bias. Heyting *et al.* [4], and most recently Scharfstein *et al.* [5], review methods for modeling dropouts in randomized-controlled trials. Hollis and Campbell [6] provide a summary of various methods used for dealing with missing data in ITT analysis in four major medical journals: *British Medical Journal*, *Lancet*, *Journal of the American Medical Association*, and *The New England Journal of Medicine*. They found that 75 per cent of the trials had some missing data for the primary outcome, and the methods used to deal with it were generally inadequate. The methods for handling missing data, in the order of most used, were: (a) complete case analysis, in which all patients with a missing response were excluded; (b) available case analysis, where all available information on each subject was used; (c) and imputing values for missing responses. The imputation methods used were last observation carried forward; explicit allocation of poor outcomes; or implicit assumptions of good or poor outcomes that include subjects with missing responses in the denominator but not in the numerator. They found only one paper that examined the effect of missing data using a range of methods for handling missing outcomes. All the above approaches, explicitly or implicitly, make assumptions about the nature of the missing data. However, different approaches may be appropriate in different situations, hence no consensus exists about how the missing responses should be handled in the ITT analysis. Therefore, it is important that sensitivity analysis be performed over a range of assumptions about the dropout mechanism [7–12].

There are three general approaches for analyzing trials with missing data. For example, Scharfstein *et al.* [5, 13] and Rotnitzky *et al.* [14, 15], adopted a selection model approach; Little [16] and Little and Rubin [17] used a pattern-mixture design; while Wu and Carroll [18] and Wu and Bailey [19, 20] use a shared-parameter model. The selection model and the pattern-mixture model approaches arise from different partitions of the observables $y$ and the missing-data indicator $R$. Selection models partition the joint distribution of $\Pr(Y, R)$ as the product of $\Pr(Y)$ and $\Pr(R|Y)$ [21]. They require explicit modeling of the missing-data mechanism where the probability that a subject would drop out may depend on the observed and unobserved values. Pattern-mixture models, on the other hand, express the joint distribution as the product of $\Pr(Y|R)$ and $\Pr(R)$ where the data are stratified by the dropout patterns with distinct model parameters for each stratum [22]. The marginal estimates in pattern-mixture models can be derived as a weighted average across pattern specific estimates [23] or by using multiple imputation [24]. Regardless of which model is used, additional assumptions or data are needed to identify the parameters in



DOI: 10.1002/sim

the joint distribution. These assumptions rely heavily on expert opinions about plausible ranges for non-identifiable parameters and are usually followed with sensitivity analysis. For example, Baker [25], Kenward [26] and Scharfstein *et al.* [5] made assumptions about the selection model to identify the parameters. In a pattern-mixture setting, Little and Wang [27], Daniels and Hogan [28], and Kenward *et al.* [29] identified parameters using constrains. Lastly, the share-parameter models are identified by using common random effects to relate the response with missing-data indicator Follmann and Wu [30], Hogan and Laird [31], and Guo *et al.* [32]. For detailed literature review on analyses with missing data, see Little [23], Kenward and Molenberghs [33], and Thijs *et al.* [34].

Here we propose a Bayesian pattern-mixture model for ITT analyses of binary outcomes in randomized trials with dropouts. Pattern-mixture models are increasingly used for such analysis as they do not require specific modeling of the dropout mechanism, and the estimates of the identified parameters are not affected by the nature of the dropout. We believe it is easier for an investigator to quantify the differences between the dropouts and the completers than to decide what can be quantified from a selection model or share-parameter model (Kaciroti *et al.* [35, 36]). Thus, we propose a new Bayesian parameterization that identifies the pattern-mixture model by comparing the dropouts with completers. The parameterization is defined as *the odds ratio of having an endpoint between the subjects who dropped out and those who completed the study*. It is easy to use in sensitivity analysis; accommodates modeling of different types of missing data, including ones missing not at random (MNAR); and contains other available methods as special case. It is also intuitively appealing to an expert, who could provide a practical range for such a parameter, which otherwise cannot be estimated from the data. Because the sensitivity parameter is unknown it is appropriate to provide a range rather than a point estimate [13, 37]. We incorporate a range on the sensitivity parameter by introducing a prior distribution (probabilistic range) and then applying Bayesian modeling strategies to derive inferences [38]. From a Bayesian perspective the inferences are derived using the Markov chain Monte Carlo (MCMC) [39, 40] simulations where values of parameters of interest are drawn multiple times from their posterior distribution. The new model is applied to the TRial Of Preventing HYpertension (TROPHY).

This paper is organized as follows. In Section 2, we describe the TROPHY study, which motivated and provided the context for the methods discussed throughout. In Section 3 we develop the Bayesian approach used for sensitivity analysis. In Section 4 we apply the proposed models. Conclusions are given in Section 5.

## 2. MOTIVATION: TROPHY STUDY

The TROPHY [41] was an investigator-initiated study to examine whether early treatment of prehypertension might prevent or delay the development of subsequent hypertension. Our primary objective was to determine whether for patients with prehypertension, 2 years of treatment with candesartan (at a dose of 16 mg daily) will reduce the incidence of hypertension for up to two years after active treatment is discontinued.

This 4-year, multicenter, randomized study involved untreated participants aged 30–65 having blood pressure in the high normal range, according to the classification developed by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) [42]. The run-in period consisted of three consecutive weekly clinic visits where blood pressure readings were obtained. Participants were considered eligible for the trial if they were not



DOI: 10.1002/sim

being treated for hypertension, their blood pressure at the first visit was lower than 160/100 mmHg, and their average of the three blood pressure readings at the three visits was a systolic pressure 130–139 mmHg and a diastolic pressure 89 mmHg or lower, or a systolic pressure 139 mmHg or lower and a diastolic pressure 85–89 mmHg. Participants who met these criteria were randomized to double-blind treatment, with candesartan (at a dose of 16 mg daily) or a matching placebo. The study consisted of, first a 2-year double-blind, placebo-controlled phase; followed by a 2-year phase in which all study patients received placebo. Subjects were examined every 3 months, as well as 1 month after the randomization, and 1 month after the first 2-year period. At each clinic visit, three sitting, resting blood pressures were obtained with an automated device (HEM-705 CP, Omron Healthcare) and averaged. Throughout the second 2-year phase, study investigators continued to remain blind to each patient's initial treatment assignment. No goal for the blood pressure was set, and a participant's treatment regime could be changed only if hypertension developed. For further details about the TROPHY study see Julius *et al.* [41, 43].

All study participants received individualized, lifestyle modification counseling at each clinic visit. Consequently, every participant had at least two lifestyle modification training sessions prior to initiation of pharmacological treatment. Thus, the TROPHY study protocol was consistent with the JNC 7 [44] recommendation: that lifestyle modification comprises the initial management of prehypertension without compelling indications, and that it precedes pharmacotherapy for onset of hypertension.

### *2.1. Primary endpoint*

The development of hypertension was chosen as the primary study endpoint. It was defined as the first occurrence of one of the following outcomes: (i) an average of three measurements of systolic pressure of 140 mmHg or higher and/or diastolic pressure of 90 mmHg or higher at any three visits during the four years of the study; (ii) an average of three measurements of BP $>160$ and/or $>100$ mmHg at any visit during four years; (iii) an average of three measurements of BP $>140$ and/or $>90$ mmHg at the end of the study; and (iv) patients requiring pharmacological treatment as decided by the attending physician. After an endpoint was reached, antihypertension treatment with metoprolol (Troprol XL, AstraZeneca), at a dose of 50 mg daily, or hydrochlorothiazide (Microzide, Watson), at a dose of 12.5 mg daily, was offered at no cost. However, study physicians were allowed to prescribe other medications, with the exception of angiotensin-receptor blockers.

The 'three times in 4 years' definition of hypertension has been criticized [45, 46] because this definition of treatment-requiring hypertension differs from widely accepted guidelines for initiation of pharmacotherapy. In the original report [41] we were committed to use this prespecified definition. Later, we reanalyzed the data using the contemporary definition of hypertension based on the guidelines published in the Seventh Report of the Joint National Committee on Hypertension [44]. Following the new guidelines, patients with an average clinic reading of systolic 140 mmHg or higher and/or diastolic of 90 mmHg or higher on two consecutive clinic visits are now considered to need treatment for hypertension. In addition, as in the initial definition, the endpoint of hypertension could also be declared if an average pressure during a single clinic visit was $>160$ mmHg systolic and/or $>100$ mmHg diastolic, or if a clinical investigator decided to initiate pharmacological treatment. Previously, an average blood pressure $>140$ systolic and/or $>90$ mmHg diastolic at the last study visit (4 years) had been also considered hypertension. This category was automatically eliminated by the new 'two consecutive high readings' definition.



DOI: 10.1002/sim

TROPHY results are published under both definitions [43, 47]. We will focus here on the sensitivity analysis following the ITT principle for the endpoint definition of hypertension, following the JNC 7 guidelines (as described at the beginning of Section 2.1).

### *2.2. Missing data*

The ITT population for the study consisted of 772 patients enrolled at 71 centers in the United States, randomly assigned to one of two groups: candesartan (391) or placebo (381). Among the 772 participants, 109 (54 in placebo) dropped out of the study before having developed hypertension. The average time in the study for these subjects was 1.1 years in the placebo group, which was smaller than the 1.75 years in the candesartan group ($p$-value $= 0.001$). When the new definition of hypertension is used, 92 subjects classified as having hypertension based on the original definition did not satisfy the new definition (JNC 7). Following the protocol, these subjects received antihypertension treatment after they become hypertensive (per original definition). Therefore, they are censored at the time the treatment was initiated and their primary outcome is considered missing for the analysis using the new endpoint definition. In addition, two subjects who had dropped out satisfy the new endpoint definition. Thus, the number of subjects with missing endpoint following the new definition is increased to 199 (101 in placebo). The average time in the study for these subjects was 1.7 years in the placebo group and 2.1 years in the candesartan group ($p$-value $=$ 0.005). Because the dropout subjects in the candesartan group were observed for a longer period and were hypertension free during this whole period, they potentially would be less likely to have hypertension at the end of the study, compared with the dropouts in the placebo group. Finally, the dropout subjects did not differ by group with respect to their baseline characteristics except for triglyceride levels, which were higher for the dropouts in the placebo group; Table I.

Table I. Baseline characteristics of dropout subjects by group.*

| Baseline measures | Placebo ($n=101$) | Candesartan ($n=98$) | $p$-Value |
|---|---|---|---|
| Age–years | 48.0±9.3 | 47.6±8.4 | 0.73 |
| Sex male–$n$ (per cent) | 60 (61.2) | 66 (65.4) | 0.56 |
| Race white–$n$ (per cent) | 78 (77.2) | 72 (73.5) | 0.11 |
| Race–$n$ (per cent) | | | |
| White | 78 (77.2) | 72 (73.5) | 0.62 |
| Black | 14 (13.9) | 17 (17.4) | 0.56 |
| Other | 9 (8.9) | 9 (9.1) | 0.99 |
| BMI–kg | 30.1±5.6 | 29.8±5.1 | 0.68 |
| Blood pressure–mm Hg | | | |
| Home SBP/DBP | 133.6±8.5/82.9±5.2 | 134.7±8.3/82.8±5.6 | 0.36/0.89 |
| Clinic SBP/DBP | 133.5±4.4/84.2±4.6 | 133.6±4.8/85.0±3.8 | 0.88/0.18 |
| Cholesterol–mg/dl | 209.0±44.9 | 202.0±38.3 | 0.24 |
| Triglycerides–mg/dl | 172.4±132.8 | 140.6±87.4 | 0.05 |
| HDL cholesterol–mg/dl | 49.1±14.6 | 47.2±12.8 | 0.33 |
| Glucose–mg/dl | 94.8±10.4 | 95.4±9.5 | 0.66 |
| Insulin–IU | 12.5±9.7 | 10.8±7.1 | 0.17 |
| Insulin:Glucose ratio | 16.9±12.8 | 14.6±9.3 | 0.16 |
| Creatine | 0.87±.20 | 0.84±.16 | 0.21 |

*Means ± SD or number (per cent).



DOI: 10.1002/sim

Based on these results we have no evidence that at the end of 4 years, dropouts in the placebo group would have a higher rate of hypertension compared with dropouts in the candesartan group. If anything, the shorter follow-up period and the higher triglyceride levels for the dropouts in the placebo group could potentially indicate higher risk for hypertension at the end of the study than for the dropouts in the candesartan group.

## 3. THE PROPOSED METHOD

In this section we propose a new parameterization within the pattern-mixture model framework to analyze binary data in randomized clinical studies with dropouts. This new parameterization accommodates modeling of different types of missing data, including those that are potentially MNAR. The parameterization is intuitive, easily used for sensitivity analysis, and contains the other available approaches as special cases. First, we introduce the complete data model for analyzing binary data and then extend it to situations with missing data.

### *3.1. Complete data model*

In the TROPHY study, we model the odds of subjects in placebo and candesartan groups developing hypertension. We use a logistic regression model with random effects to account for clustering within a center (or physician), and test whether the odds differ for the two groups. Let $Y_{ij}$ be the binary measure of the primary endpoint, which is 1 if the subject $j$ under the care of physician $i$ develops hypertension during the 4-year period and 0 otherwise; and let $p_{ij}=\Pr(Y_{ij}=1)$ be the probability of developing hypertension. The distribution of $Y_{ij}$ conditioned on the random effect $b_i$ is Bernoulli with probability $p_{ij}$, modeled by

$$\text{logit}(p_{ij}|\text{Trt}_{ij}, b_i)=\beta_0+\beta_1*\text{Trt}_{ij}+b_i \tag{1}$$

where $b_i \sim N(0, \sigma_b^2)$ is a random intercept to account for clustering of subjects by physician; and $\text{Trt}_{ij}$ is a treatment indicator equal to 1 if subject $j$ under the care of physician $i$ was in candesartan group and 0 otherwise. Other covariates can be included in the model if needed as additional predictors for the adjusted analysis. The primary parameter of interest is $\beta_1$, tested via the null hypothesis of no treatment effect $H_0:\beta_1=0$. MCMC simulations are used to construct inferences based on the values drawn from the joint posterior distribution

$$\Pr(\beta, b|y, \text{Trt})=\prod_{i=1}^{K}\prod_{j=1}^{n_i}\Pr(y_{ij}|\text{Trt}_{ij}, \beta, b_i)\phi(b_i)p(\beta)=\prod_{i=1}^{K}\prod_{j=1}^{n_i}\frac{e^{(\beta_0+\beta_1*\text{Trt}_{ij}+b_i)*y_{ij}}}{1+e^{\beta_0+\beta_1*\text{Trt}_{ij}+b_i}}\phi(b_i)p(\beta)$$

where $\phi(b_i)=(2\pi\sigma_b^2)^{-1/2}\exp(-b_i^2/2\sigma_b^2)$. Population average (PA) estimates are derived from the subject-specific estimates by integrating out the random effects

$$\Pr(\beta^{(\text{PA})}|y, \text{Trt})=\int\prod_{i=1}^{K}\prod_{j=1}^{n_i}\frac{e^{(\beta_0+\beta_1*\text{Trt}_{ij}+b_i)*y_{ij}}}{1+e^{\beta_0+\beta_1*\text{Trt}_{ij}+b_i}}\phi(b_i)p(\beta)\,db$$

The integral does not have a closed form. Thus, the $\beta^{(\text{PA})}$ parameters are calculated by using either the MCMC computational power or the following approximation: $\beta^{(\text{PA})}\approx a*\beta$, where



DOI: 10.1002/sim

$a=(1+(16\sqrt{3}/15\pi)^2\sigma_b^2)^{-1/2}=(1+0.346\sigma_b^2)^{-1/2}$; here $a$ is the attenuation factor that is $<1$ [48, 49]. For numerical simplicity we used the approximation approach, which works very well.

### *3.2. Logistic regression with missing data*

When a subject in a randomized clinical trial drops out before the study ends with no endpoint at the time of dropout, excluding that person from the analysis potentially will affect the randomization. An analysis using the ITT principle includes such subjects in its final inferences to maintain randomization. The true reasons for dropping out are often unknown, so methods that can handle missing data for a variety of missing-data mechanisms are useful. We propose here a Bayesian model using pattern-mixture framework to analyze the data with dropouts potentially generated from an MNAR missing-data mechanism. MNAR mechanisms imply that the distribution of the primary endpoint variable for the respondents and non-respondents is systematically different, even after controlling for all known covariates. In such situations, the inferences based on the likelihood function of the observed data, while ignoring the missing-data mechanism, would not be valid. Here we use a proper Bayesian prior distribution to identify the proposed model. In general, under a pattern-mixture model the parameters are allowed to vary by pattern $r$. Thus, let $\beta^{(r)}$ denote the parameters of model (1) for pattern $r$, with $r=0$ corresponding to completers and $r=1$ to dropouts, with $\beta^{(1)}\neq\beta^{(0)}$ for MNAR mechanism. Because there are no data to estimate all the parameters in the missing pattern $r=1$, the model is underidentified. Thus, restriction or prior information about the model is required to fully identify the parameters. Following Rubin [22] and Little and Rubin [17], we identify the model by specifying a prior distribution $p(\beta^{(1)}|\beta^{(0)})$ on the parameters of the missing pattern conditioned on the parameters of the observed pattern. Because, in general, less is known about parameters $\beta^{(1)}$ of the missing-data pattern than about the missing data themselves, putting constraints on the missing data will provide an intuitive framework to perform sensitivity analysis. Kaciroti *et al.* [35, 36] use between-pattern differences on ordinal and count outcome variables to characterize different missing-data mechanisms. Here we propose a similar framework for binary outcomes with data MNAR by relating the distribution of the missing data to the distribution of the observed data and translating it into a prior distribution of $p(\beta^{(r)}|\beta^{(0)})$. To identify the model, using a Bayesian approach, we compare the odds of having an endpoint in the missing-data pattern to the odds of having an endpoint in the observed data pattern.

Specifically, let $p^{(r)}=\Pr(Y=1|\text{Trt},\beta^{(r)},b)$ for pattern $r$. Then, there exists some parameter $\tilde{\lambda}(\text{Trt})$, such that for $r=0,1$:

$$\frac{p^{(1)}}{1-p^{(1)}}=\tilde{\lambda}(\text{Trt})\frac{p^{(0)}}{1-p^{(0)}} \tag{2}$$

In this case, $\tilde{\lambda}(\text{Trt})$ is the odds ratio statistics between the missing-data pattern and the complete data pattern, and is thus a measure of the departure from missing at random (MAR). We assume that $\tilde{\lambda}$ has a distribution with mean $l$ and variance $c^2*l^2$, where $c$ is the coefficient of variation. In this approach, the uncertainty of the relationship between the distribution of the missing data and the distribution of the observed data is captured by the prior distribution (probabilistic range) given to $\tilde{\lambda}$. Such uncertainty is incorporated into the estimation of $\beta^{(1)}$ through a Bayesian approach. Then in the proposed Bayesian model, $\tilde{\lambda}(\text{Trt})$ can be seen as an ignorability index equal to 1 when the missing data are MAR, and different from 1 when the missing data are MNAR. The advantages



DOI: 10.1002/sim

of this approach are in the simplicity and the clarity of the underling statistical assumption used to identify the model. It is intuitive and easy to understand for an expert and provides a useful and practical framework for sensitivity analysis over a range of missing-data mechanisms.

To identify the model [17, 22] we introduce an informative prior $p(\beta^{(1)}|\beta^{(0)})$ that is derived based on the prior distribution of $\tilde{\lambda}$. Following (2) we have

$$e^{\beta_0^{(1)}+\beta_1^{(1)}*\mathrm{Trt}_i+b_i}=\tilde{\lambda}(\mathrm{Trt}_i)e^{\beta_0^{(0)}+\beta_1^{(0)}*\mathrm{Trt}_i+b_i} \tag{3}$$

Let $\tilde{\lambda}_k=\tilde{\lambda}(\mathrm{Trt}=k)$ be the odds ratio statistic between the missing-data pattern and the observed data pattern for the subgroup identified by $\mathrm{Trt}=k$ for $k=0, 1$ Then

$$e^{\beta_0^{(1)}}=\tilde{\lambda}_0 e^{\beta_0^{(0)}}$$

and

$$e^{\beta_0^{(1)}+\beta_1^{(1)}}=\tilde{\lambda}_1 e^{\beta_0^{(0)}+\beta_1^{(0)}}$$

or

$$\beta_0^{(1)}=\log(\tilde{\lambda}_0)+\beta_0^{(0)} \tag{4}$$

and

$$\beta_1^{(1)}=\log(\tilde{\lambda}_1)-\log(\tilde{\lambda}_0)+\beta_1^{(0)} \tag{5}$$

From (4) and (5) the prior distribution, $p(\beta^{(1)}|\beta^{(0)})$, is defined based on the distributions of $\tilde{\lambda}_0$ and $\tilde{\lambda}_1$. Thus, the identifiability of the pattern-mixture model is translated into defining a distribution on $\tilde{\lambda}_0$ for the placebo group and $\tilde{\lambda}_1$ for the candesartan group. Giving a distribution to $\tilde{\lambda}_k$ is easy to understand and enables us to derive inferences over a class of MNAR missing-data mechanisms. For instance, $\tilde{\lambda}_0 \sim$ log-normal with mean $l_0=0.5$, and $c=0.1$ indicates that, on average for a dropout in the placebo group, the odds of developing hypertension are half (95 per cent CI$=(0.41, 0.61)$) of that for a subject who completed the study. Inferences derived based on this $\tilde{\lambda}_0$ would be true even when the missing data are MNAR but within the range identified by $\tilde{\lambda}_0$. The $c$ parameter captures any uncertainty related to the missing-data mechanism, that is, the range of $\tilde{\lambda}_0$. For instance, in the above example if $c=0.5$, the 95 per cent CI of $\tilde{\lambda}_0$ would be wider: 95 per cent CI$=(0.16, 1.16)$. If $c=0$, then the distribution of $\tilde{\lambda}$ is degenerate, which results in a deterministic constraint. Under this framework, the model is identified using both $l_k$ and the $c$ parameters, which then can be used for sensitivity analysis. The model with data MAR is a special case, where $\tilde{\lambda}_k \equiv 1$, for $k=0$, 1, and $c=0$.

The log-normal distribution family is an attractive choice for $\tilde{\lambda}_k$ as it yields a normal prior distribution for $\beta^{(r)}$, though other distributions for $\tilde{\lambda}_k$ are also possible. Then MCMC methods could be used to construct inferences based on values drawn from the following joint posterior distribution

$$\Pr(\beta^{(0)}, \beta^{(1)}, b|y, \mathrm{trt}) = \prod_{i,j\in\mathscr{P}_0} \frac{e^{(\beta_0^{(0)}+\beta_1^{(0)}*\mathrm{Trt}_i+b_i)*Y_{ij}}}{1+e^{\beta_0^{(0)}+\beta_1^{(0)}*\mathrm{Trt}_i+b_i}} p(\beta^{(0)}) \times \prod_{i,j\in\mathscr{P}_1} \frac{e^{(\beta_0^{(1)}+\beta_1^{(1)}*\mathrm{Trt}_i+b_i)*Y_{ij}}}{1+e^{\beta_0^{(1)}+\beta_1^{(1)}*\mathrm{Trt}_i+b_i}} p(\beta^{(1)}|\beta^{(0)})\phi(b_i)$$



DOI: 10.1002/sim

where $\mathscr{P}_0$ is the set of subjects who completed the study, $\mathscr{P}_1$ is the set of subjects who dropped out, and $\phi(b_i)=(2\pi\sigma_b^2)^{-1/2}\exp(-b_i^2/2\sigma_b^2)$. The first factor corresponds to the posterior distribution of the observed data, assuming a non-informative prior distribution $p(\beta^{(0)})$, and is orthogonal to the second factor. The second factor corresponds to the posterior distribution of the missing data and assumes an informative prior distribution $p(\beta^{(1)}|\beta^{(0)})$. The $p(\beta^{(1)}|\beta^{(0)})$ is defined from the distributions of $\tilde{\lambda}_1$ and $\tilde{\lambda}_0$ following equations (4) and (5).

Finally, the posterior distribution of the overall parameters represents a mixture of distributions of parameters corresponding to the complete data and dropout patterns. Thus, draws of the overall parameters are derived using a weighted average of the corresponding draws of parameters for each pattern, with the weights equal to the proportion of subjects in each (Little [23]). The final inferences are derived using MCMC method that is implemented using WinBUGS1.4 software [50]. Finally, an added benefit of the proposed method is that multiple draws are available for the missing data, which then can be used for any other analysis within the multiple imputation framework.

## 4. APPLICATION

The sensitivity analysis method developed in Section 4 was applied to the data from the TROPHY study. The effect of a 2-year treatment with candesartan 2 years after stopping such treatment, compared with a placebo, is estimated based on the logistic regression model (1), including a random intercept for the physician. Different scenarios for the dropouts, including commonly used assumptions in ITT analysis, are considered to assess the effect of the dropouts on the final results. In addition, sensitivity analysis, based on assumptions that make the treatment effect borderline significant (BS), is also included. Following is a list of six different scenarios for sensitivity analysis starting from the most favorable for the candesartan group, to the least favorable. We set $c=0.1$, except for scenario 2 where $c=0$, which is equivalent to a MAR missing-data mechanism.

1. $l_0\to\infty, l_1\to 0 \Rightarrow p_0^{(1)}\to 1$ and $p_1^{(1)}\to 0$. Here patients in the placebo group who dropped out are considered as to have hypertension, and patients who dropped out from the candesartan group are considered hypertension free. In this scenario, the incidence of hypertension in the placebo group is overestimated, while underestimated in the candesartan group. Hence the best case scenario (BCS) is in favor of candesartan.
2. $l_k=1, c=0 \Rightarrow p_k^{(1)}=p_k^{(0)}$, this indicates that in each group the incidence of hypertension among the dropouts is the same as for those who completed the study. This is equivalent to data MAR assumption.
3. $l_k\to\infty \Rightarrow p_k^{(1)}\to 1$, this is equivalent to considering the dropouts as endpoints (DAE). Under this scenario, the incidence of hypertension is overestimated for each group.
4. $l_k\to 0 \Rightarrow p_k^{(1)}\to 0$, this is equivalent to considering the dropouts hypertension free at the end of the fourth year. It is often referred to as the last-observation-carried-forward (LOCF) approach. Here the value of the primary endpoint at the end of the study is set to be the same as the last observed value. It assumes that in the absence of observed hypertension, a subject is considered hypertension free. Under this scenario, the incidence of hypertension is underestimated in each group.



DOI: 10.1002/sim

5. $l_k = \bar{l}_k$, where $\bar{l}_k$ are chosen in such a way that the effect of candesartan at 4 years is BS where $p = 0.05$. Such sensitivity analysis is important as it shows how different the dropout subjects must be from the observed subjects for the candesartan effect to become non-significant.
6. $l_0 \to 0, l_1 \to \infty \Rightarrow p_0^{(1)} \to 0$ and $p_1^{(1)} \to 1$. Here patients who dropped out in the placebo group are considered hypertension free and patients who dropped out from the candesartan group are considered to have hypertension. The incidence of hypertension in the placebo group is underestimated, but is overestimated in the candesartan group. Hence the worst-case scenario (WCS).

The incidence of hypertension for each group under the above scenarios and the $p$-value for group comparisons are shown in Table II. The results are for PA inferences where the random intercept is integrated out. The estimate of the variance for the random intercept is $\sigma_b^2 = 0.33(0.08 - 0.75)$.

In Figure 1 we give the ORs of candesartan effect under the different scenarios. An OR less than 1 favors the candesartan group and an OR larger than 1 favors the placebo group. The sensitivity analysis shows that the effect of candesartan varies by the assumptions used for the dropouts, with OR ranging from 0.21 (BCS) to 1.87 (WCS). However, if the same assumptions are used in both groups (scenarios 2, 3, and 4), the effect of candesartan in reducing the incidence of hypertension is strong 2 years after ceasing of treatment. The effect of candesartan would decrease if the candesartan dropout patients compared with the completers were at higher risk of hypertension than those in the placebo group. For example in BS*a* scenario, when the dropouts in candesartan group are 4.5 times more likely to develop hypertension than completers, but in placebo group the dropouts are just as likely as completers, the effect of candesartan becomes BS. In scenarios BS*d* and BS*e*, the assumptions about the dropouts favor the placebo group to the degree that the effect of the placebo becomes borderline significantly better than the effect of the candesartan. Specifically in BS*c*, when all dropouts in the placebo group are considered non-hypertensive, whereas in candesartan group the dropouts are considered 60 per cent more likely to develop hypertension than completers, the risk of hypertension will be reduced for the placebo group compared with the candesartan group; OR = 1.34 and is BS. Under the WCS, the protective effect of placebo on reducing the risk of hypertension is strongest; OR = 1.87 (95 per cent CI = (1.44–2.40)).

Table II. Sensitivity analysis under different dropout mechanisms.*

| | | Placebo $p$ (95 per cent CI) | Candesartan $p$ (95 per cent CI) | $p$-Value |
|---|---|---|---|---|
| 1. $l_0 \to \infty,\ l_1 \to 0$ | (BCS) | 78.7 (73.9–83.2) | 43.1 (37.9–48.4) | <0.001 |
| 2. $l_0 = l_1 = 1, c = 0$ | (MAR) | 71.4 (64.9–77.4) | 57.0 (50.1–63.9) | 0.001 |
| 3. $l_0 = l_1 \to \infty$ | (DAE) | 78.7 (73.9–83.2) | 67.4 (62.3–72.6) | 0.001 |
| 4. $l_0 = l_1 \to 0$ | (LOCF) | 52.8 (48.0–57.2) | 43.0 (37.9–48.3) | 0.001 |
| 5a. $l_0 = 1,\ l_1 = 4.5$ | (BS*a*) | 71.3 (64.8–77.4) | 63.9 (57.8–69.9) | 0.050 |
| 5b. $l_0 = 0.35,\ l_1 = 1$ | (BS*b*) | 65.0 (58.1–71.6) | 56.9 (49.9–63.9) | 0.050 |
| 5c. $l_0 = 0.6,\ l_1 = 2$ | (BS*c*) | 68.4 (61.5–74.9) | 60.7 (54.0–67.3) | 0.050 |
| 5d. $l_0 \to 0,\ l_1 = 1.6$ | (BS*d*) | 52.8 (48.1–57.2) | 59.6 (52.7–66.4) | 0.050 |
| 5e. $l_0 = 0.17,\ l_1 \to \infty$ | (BS*e*) | 60.5 (54.1–67.2) | 67.6 (62.3–72.7) | 0.050 |
| 6. $l_0 \to 0,\ l_1 \to \infty$ | (WCS) | 52.8 (48.1–57.3) | 67.4 (62.3–72.7) | 0.001 |

*Results are in per cent.



DOI: 10.1002/sim

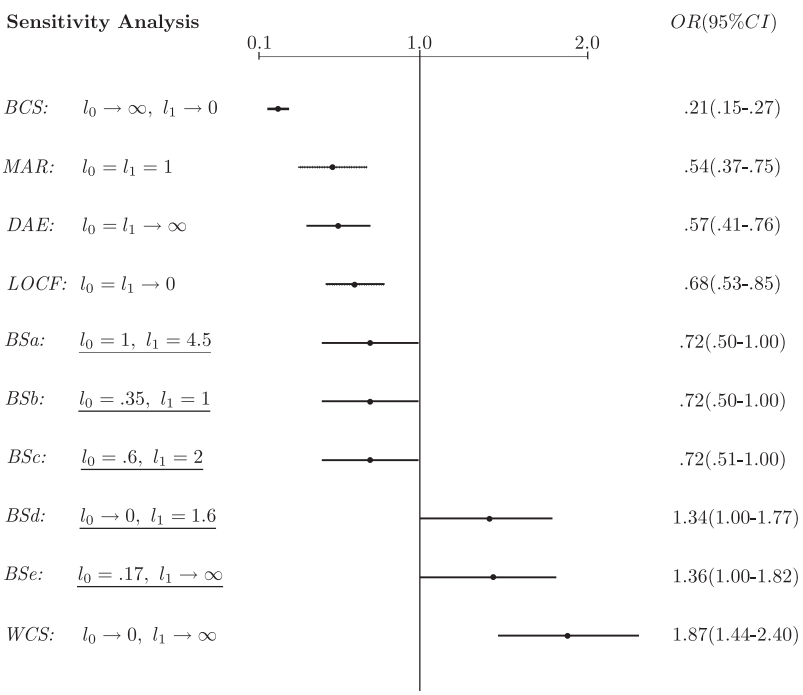


Figure 1. Graphical display of sensitivity analysis varying $l_0$ and $l_1$ and $c = 0.1$.

## 5. CONCLUSION

In randomized-controlled trials with dropouts, ITT analysis may lead to bias conclusions unless missing-data mechanism is correctly specified. Without knowledge of the missing-data mechanism sensitivity analysis is necessary to investigate conclusions over alternatives assumptions about the dropout mechanism. Both selection-models [10, 25] and pattern-mixture models [51–53] have been used for sensitivity analysis. In this paper we develop a Bayesian pattern-mixture model for incorporating dropout patients into an ITT analysis in a randomized-controlled trial where the primary outcome is binary. We approach the missing-data problem by using a pattern-mixture model, which is identified by introducing an intuitive and easy-to-use parameterization. The new parameterization, $\tilde{\lambda}$, relates the odds of having an endpoint among dropouts to the odds of having an endpoint among completers. Because there are no data to estimate the identifying parameter, sensitivity analysis is performed using different prior distributions for $\tilde{\lambda}$. Even though the distribution of $\tilde{\lambda}$ is unknown, it is possible for an expert to give a range for $\tilde{\lambda}$ and then explore the sensitivity of statistical inferences over such a range. The proposed parameterization is flexible for sensitivity analysis, easy to implement, and contains many of the available methods as special cases. The new model was applied to the TROPHY study.

Using the data from the TROPHY study, assuming an MAR missing-data mechanism, the incidence of hypertension at the end of the study showed 71.4 per cent in the placebo group and 57.0 per cent in the candesartan group. Under this scenario, 2 years of candesartan treatment can



DOI: 10.1002/sim

reduce the odds of developing hypertension 2 years later by 46 per cent. The results of sensitivity analysis displayed in Figure 1 show that inferences on the candesartan effect are sensitive to the nature of the missing data. The OR of reducing hypertension 2 years after taking candesartan differs by the assumptions made about the missing data, varying from 0.21 under the BCS, to 0.57 under the LOCF, and to an increase of 1.87 under the WCS. If the same assumptions about the dropouts are used in both groups (DAE, LOCF), the effect of candesartan is strong in reducing the incidence of hypertension 2 years after treatment. It would take large differences in the risk of hypertension among dropouts favoring placebo (BS*a*, BS*b*, BS*c*) for the effect of treatment to become BS. The placebo would do better than candesartan if the risk of hypertension among the dropouts strongly favored the placebo group (BS*d*, BS*e*, WCS). However, based on analysis in Section 2.2 such assumptions are unlikely.

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DOI: 10.1002/sim