Logistic Regression with Covariate Measurement Error in an Adaptive Design: A Bayesian Approach

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Dissertation Research
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Outline

- Motivation of Research and Literature Review
- Covariate Measurement Error
  - A Bayesian Adaptive Design Accounting for Measurement Error
- Discussion and Future Research
- References

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Motivation for Research

- Spann, M. (2006), "Bayesian Adaptive Designs for Non-Inferiority and Dose Selection Trials", Ph.D. thesis, Baylor University.

- Edmonds, J. (2008), "The Impact of a Misclassified Response on Bayesian Adaptive Designs", Chapter of Ph.D. thesis, Baylor University.

Background

- Fixed-sample designs have been and remain the most commonly used approach in phase II and phase III trials (Berry, 2001)
  - ➢ Two therapeutic arms are usually considered, enabling straightforward treatment comparisons
  - ➢ Specify a sample size to achieve appropriate sample size requirements

- Can lead to slow and unnecessarily costly development

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Adaptive Designs

- Increasingly popular in clinical trials
  - Modifications to the trial or statistical procedure are often necessary
  - Afford potentially safer and more efficient trials
  - Designs are flexible

- We are concerned with how Bayesian adaptive designs are affected by measurement error.

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Examples in the Literature

- Giles et al. (2003) used a Bayesian adaptive design to select most effective treatment for acute myeloid leukemia requiring only 34 patients.
- ASTIN study sponsored by Pfizer used an adaptive design to estimate a dose response curve to discover the 95% effective dose, (Krams et al., 2003).
- Thall and Russell (1998) used Bayesian decision criteria for dose finding and safety monitoring in Phase I/II clinical trials.
- Bekele and Shen (2005) used a Bayesian approach and a latent variable to jointly model toxicity and biomarker expression for dose finding.

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Covariate Measurement Error

- Statistical task: 'learn' the relationship between an outcome variable y and an explanatory variables x and z
  - z represents those predictors measured without error
  - x represents those that cannot be measured exactly

- A rough or *surrogate* variable w is often recorded in place of x, which complicates inference

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Covariate Measurement Error

- The parameters in the model relating y and (z,x) cannot be estimated directly by fitting y to (z,x).
- Substituting w for x, making no adjustments, leads to poor estimation of the relationship between y and (z,x).
- Goal: infer the correct relationship between y and (z,x) indirectly by fitting a model relating y and (z,x) accounting for measurement error.

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A Measurement Example

- Let x be the long-term average systolic blood pressure and y be cholesterol level
  - x is assumed to be measured with error
  - w measured systolic blood pressure
  - y cholesterol level

- w differs from x
  - Significant temporal variation
  - Instrument error
  - Reader error

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A Measurement Example

- Suppose y and x are linearly related:

$$y = \beta_0 + \beta_1 x + \varepsilon$$

- x is measured with error

- Simulate a data set, with independent errors, $\beta_0 = 145$, $\beta_1 = 1$, and $\sigma = 0.25$, along with the least squares fit for the line.

- We cannot observe x, thus we use our surrogate variable w.

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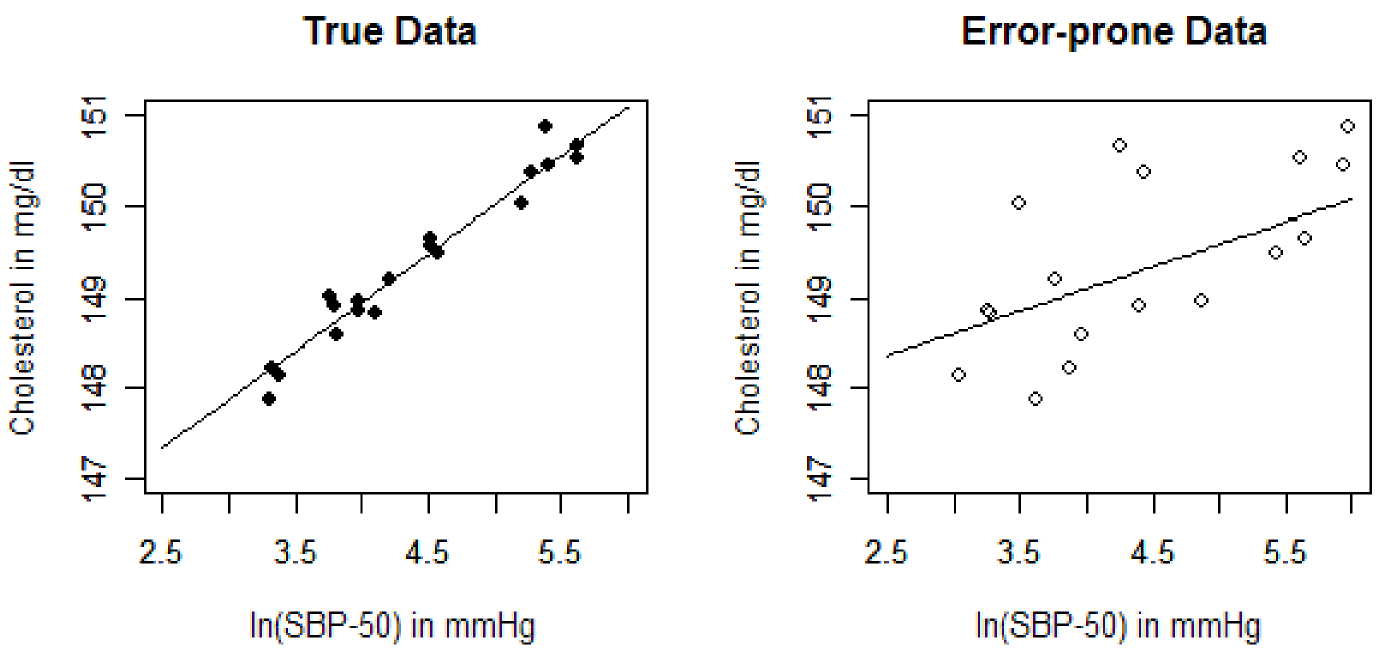
A Measurement Example



- The plots above show an attenuation (flattening) of the regression line for the error-prone data with more variability

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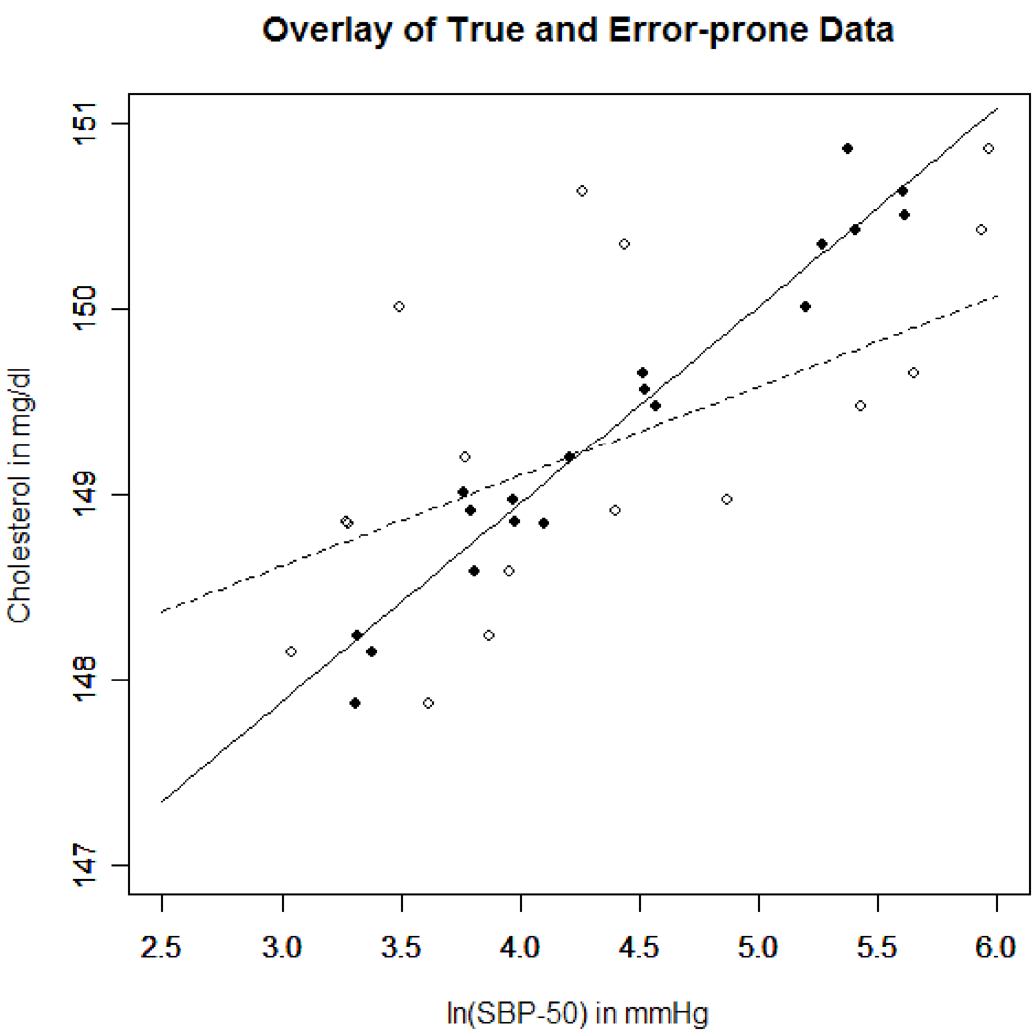
A Measurement Example



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Correcting for Measurement Error

- We must specify a parametric model for each component of the data:
  - Response model
  - Measurement error model
  - Exposure model

- When the measurement model includes classical components, we must also specify a distribution for the unobserved x given the observed z

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Measurement Error Model

- Classical Error
  - ➢ $w = x + u$ (Additive Error)
    - o w is an unbiased measure of x
    - o u is independent of x
    - o Also, $E(u|x,z) = 0$
  - ➢ $w = x \cdot u$ (Multiplicative Error)
- Choice is classical if an error-prone covariate is measured for each individual

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Non-differential Measurement Error

- w contains no information about the response other than what is available in x

- More formally: the conditional distribution of $y|x,w$ is the same as that for $y|x$.

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A Bayesian Adaptive Design Accounting for ME

- Consider an illustration for a logistic regression model demonstrating the effects of measurement error on an adaptive design

- Consider a two-arm Bayesian adaptive design for assessing superiority utilizing adaptive allocation in the context of the Framingham Study.

The Framingham Study

- Large cohort study following individuals for the development of coronary heart disease (Kannel, et al., 1986)
- Main predictor of interest is systolic blood pressure, which is assumed to be measured with error.
- As per Carroll et al. (2006), we calculate the adjusted systolic blood pressure, $\ln(SBP-50)$, where SBP is long-term average systolic blood pressure for two separate visits.

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The Bayesian Model

- For simplicity's sake, our model will include SBP, x_i, and treatment effect, t_j (1 or 0)

- The observed response for each patient is denoted by

  $\tilde{y}_{ij}, i = 1,\ldots,n_j,$ for each of two treatments, $j = 1,2$

- Let w_{ij} be the surrogate recorded for blood pressure on two separate visits

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The Bayesian Model

- Suppose a study is to have at most $n = 100$ subjects for which blood pressure, w_{ij} , and treatment response, y_{ij} , are observed for all subjects.

- Two replicate measurements for the surrogate variable, w_{ij} , are made for each subject, with the replicates being conditionally independent given the unobserved x_i.

The Bayesian Model

Consider the logistic regression model

$$\text{logit}\left(p_{ij} = 1 \mid x_i, t_j\right) = \beta_0 + \beta_1 x_i + \beta_2 t_j$$

where

$$y_{ij} \mid x_i, t_j \sim \text{Bernoulli}[\text{logit}^{-1}(\beta_0 + \beta_1 x_i + \beta_2 t_j)]$$

The Bayesian Model

- Assuming the measurement error is additive, a classical measurement model is represented by

$$w_{ij} \mid x_i, y_{ij} \sim N\left(x_i, \tau_u\right)$$

- Moreover, for the exposure model, a normal model is convenient:

$$x_i \sim N\left(\mu, \tau_x\right)$$

The Bayesian Model

- In order to proceed under the Bayesian context, we must introduce prior distributions for all unknown parameters: ($\boldsymbol{\beta}$, τ_u, τ_x)

- Assuming prior independence of all unknown parameters, the joint distribution is given by:

$$\pi(\boldsymbol{\beta}, \tau_u, \tau_x) = \pi(\boldsymbol{\beta})\pi(\tau_u)\pi(\tau_x)$$

- Moreover, the joint posterior distribution is given by:

$$\pi(\boldsymbol{\beta}, \tau_u, \tau_x \mid \tilde{\mathbf{y}}) \propto f(\boldsymbol{\beta}, \tau_u, \tau_x \mid \tilde{\mathbf{y}})\pi(\boldsymbol{\beta}, \tau_u, \tau_x)$$

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The Bayesian Model

Define the logistic regression model as

$$\text{logit}(p_{ij} \mid x_i, t_j) = m(x_i, t_j, \boldsymbol{\theta}),$$

where,

$$m(x_i, t_j, \boldsymbol{\theta}) = \log\left[\frac{\Pr(y_{ij} = 1 \mid x_i, t_j)}{\Pr(y_{ij} = 0 \mid x_i, t_j)}\right]$$

The Bayesian Model

- The likelihood is proportional to:

$$f(\tilde{\mathbf{y}} \mid \boldsymbol{\theta}) \propto \exp\left[\sum_{i=1}^{n} y_i m(x_i, t_j, \boldsymbol{\theta}) - \sum_{i=1}^{n} \log\{1 + e^{m(x_i, t_j, \boldsymbol{\theta})}\}\right]$$

- The posterior distribution is proportional to:

$$\pi[\boldsymbol{\theta} \mid x_i, t_j] \propto \exp\left[\sum_{i=1}^{n} y_i m(x_i, t_j, \boldsymbol{\theta}) - \sum_{i=1}^{n} \log\{1 + e^{m(x_i, t_j, \boldsymbol{\theta})}\}\right] \pi(\boldsymbol{\theta})$$

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The Bayesian Model

The posterior predictive distribution is proportional to:

$$\pi[y_{new} \mid \tilde{\mathbf{y}}, \mathbf{x}, \mathbf{z}] \propto \exp\left\{ \sum_{i=1}^{n} y_i m(x_i, t_j, \theta) - \sum_{i=1}^{n} \log\left[1 + e^{m(x_i, t_j, \theta)}\right] + \frac{(x_i - \alpha_0 - \alpha_1 z_i)^2}{\tau_x} + \frac{(w_i - x_i)^2}{\tau_u} \right\}$$

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Prior Distributions

- In our hierarchical model structure, we assign independent informative normal priors on β_0, β_1, and β_2 in the outcome model.

- For some unknown, positive ϕ, we assume

  $\tau_u = \phi\tau_x$ or $\tau_x = \phi\tau_u$

$$\tau_u = \begin{cases} \phi\tau_x & \tau_x \le \tau_u \\ \dfrac{1}{\phi}\tau_x & \tau_x > \tau_u \end{cases}$$

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$\lambda/(1-\lambda)$

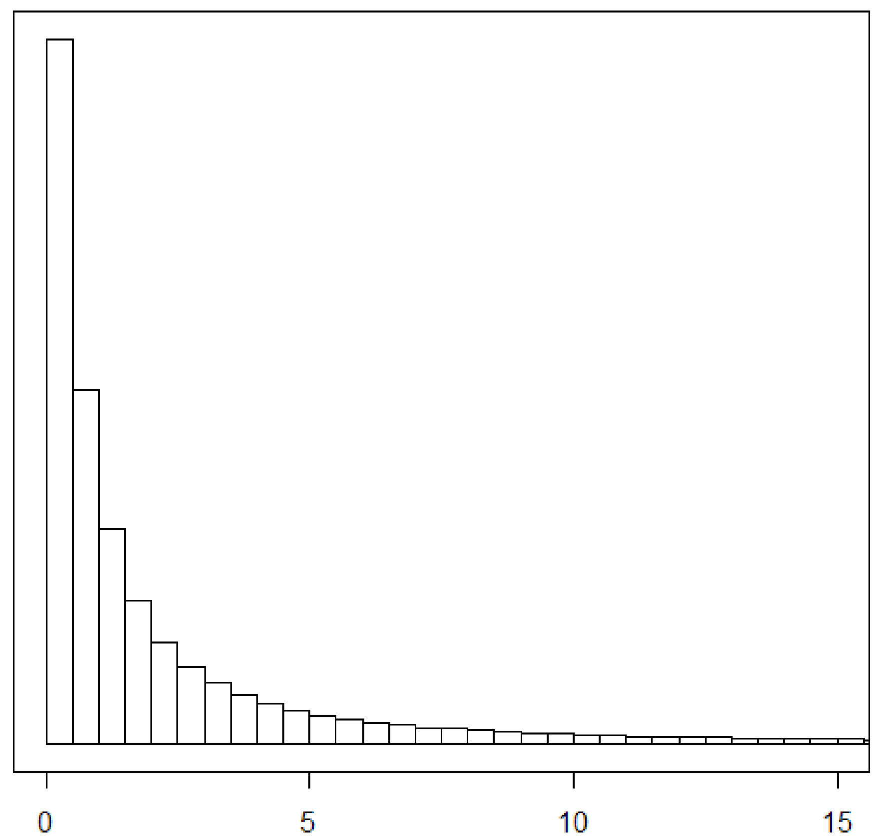
Alternative Prior Structures

- As per Carroll et al. (2006), an alternative prior structure is to take

$$\tau_u = \frac{\lambda \tau_x}{(1-\lambda)}$$

for $0 < \lambda < 1$.

Induced Prior for λ / (1-λ)



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Hierarchical Model

$$y_{ij} \sim \text{Bernoulli}[\text{logit}^{-1}(\beta_0 + \beta_1 w_i + \beta_2 t_j)]$$

$$\beta_2 \sim \text{Normal}(\mu_2, \tau_2)$$

$$w_i \sim \text{Normal}(x_i, \tau_u)$$

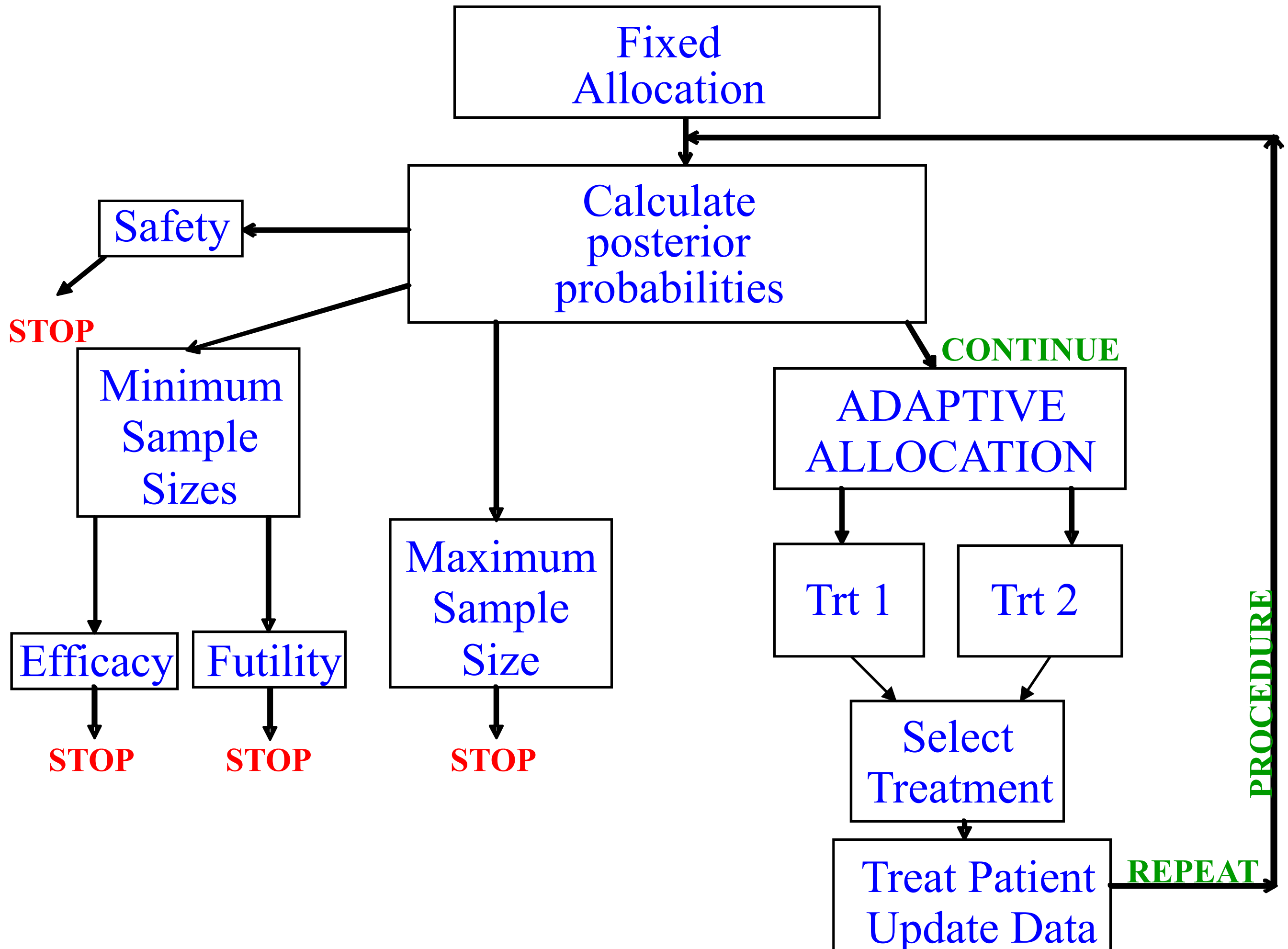
$$\beta_1 \sim \text{Normal}(\mu_1, \tau_1)$$

$$x_i \sim \text{Normal}(\mu, \tau_x)$$

$$\beta_0 \sim \text{Normal}(\mu_0, \tau_0)$$

$$\tau_x \sim \text{Gamma}(\gamma_1, \gamma_2)$$

Bayesian Adaptive Designs



Adapted from Spann(2006)

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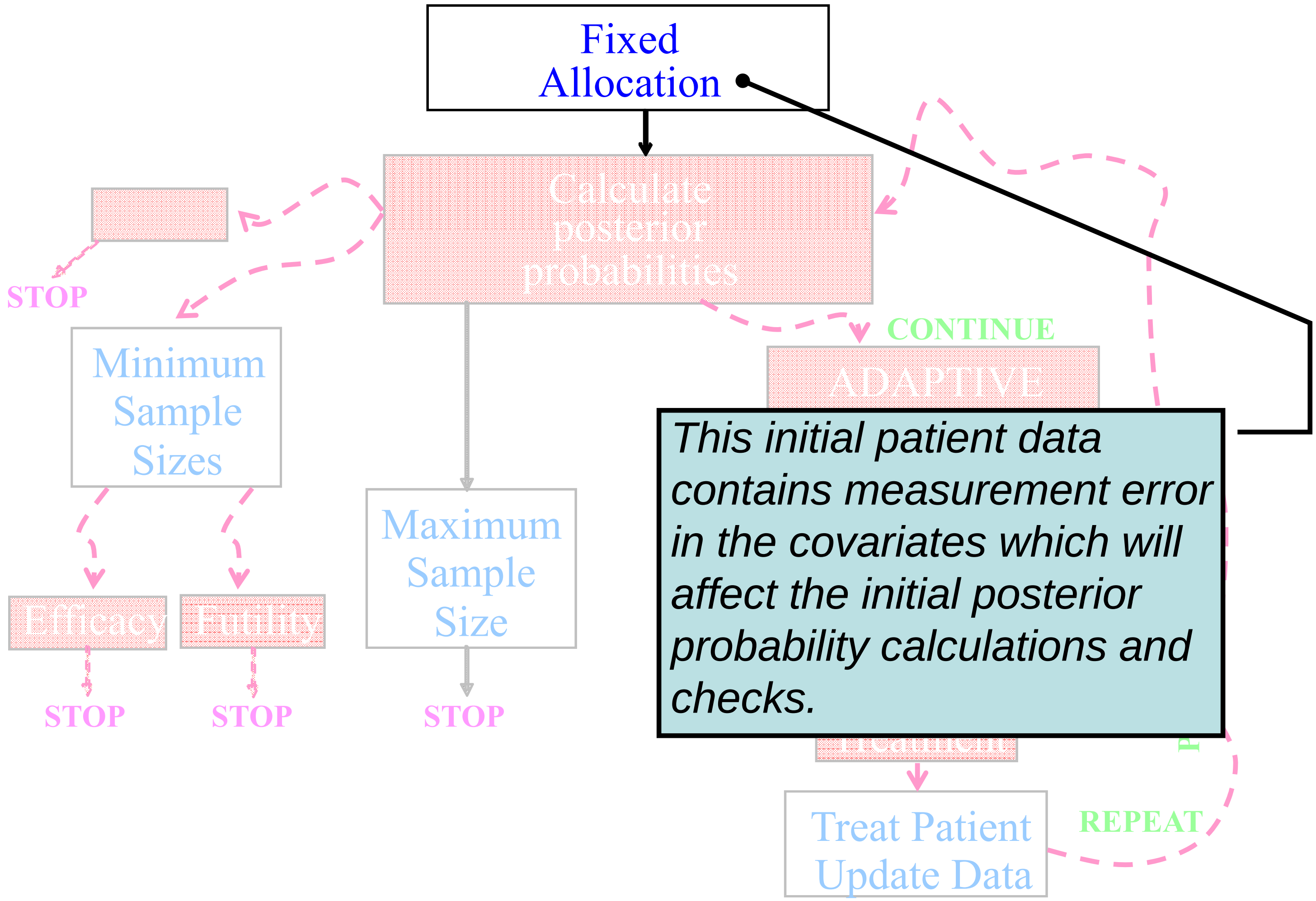
Effects of Measurement Error



This initial patient data contains measurement error in the covariates which will affect the initial posterior probability calculations and checks.

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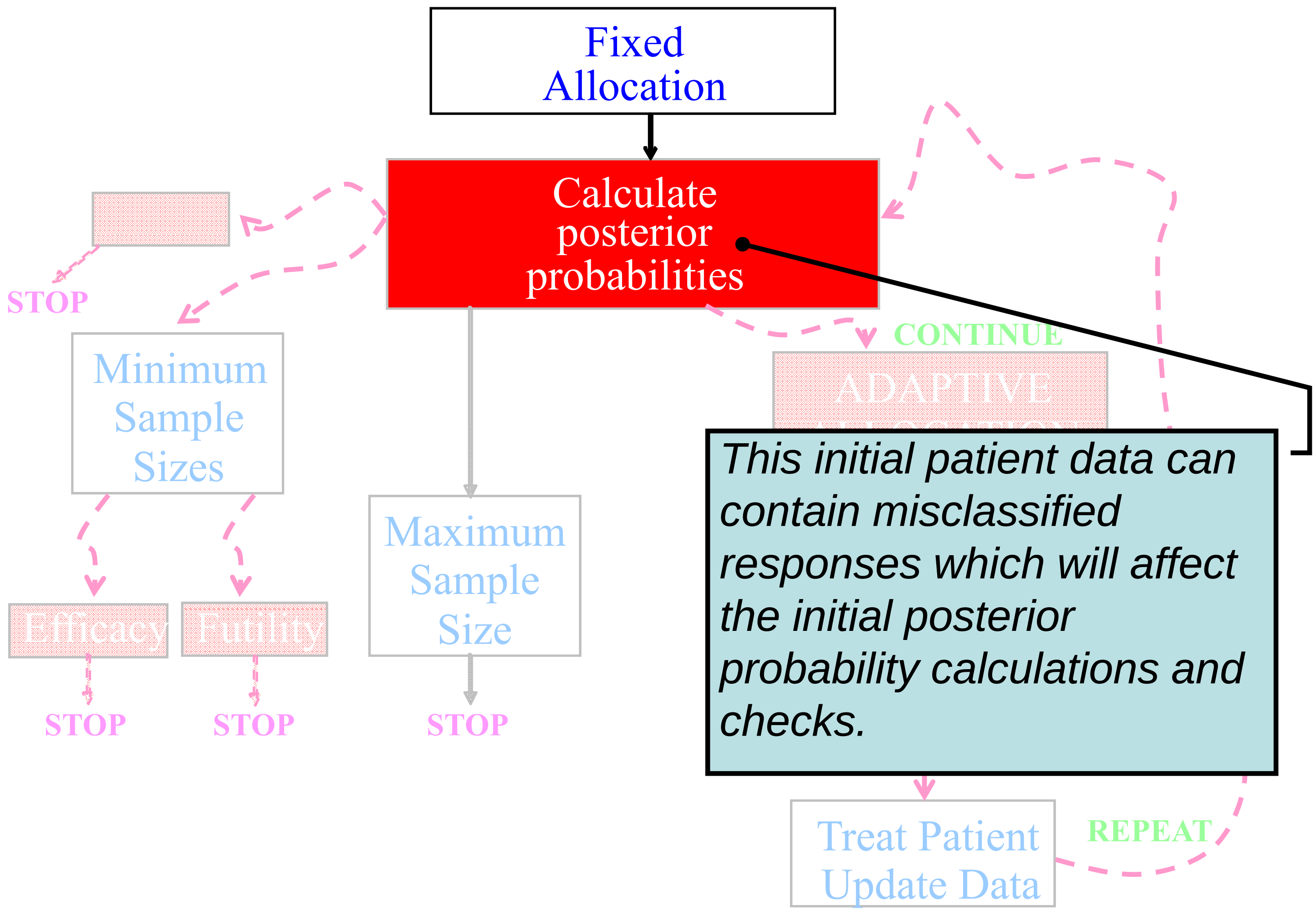
Effects of Measurement Error



This initial patient data can contain misclassified responses which will affect the initial posterior probability calculations and checks.

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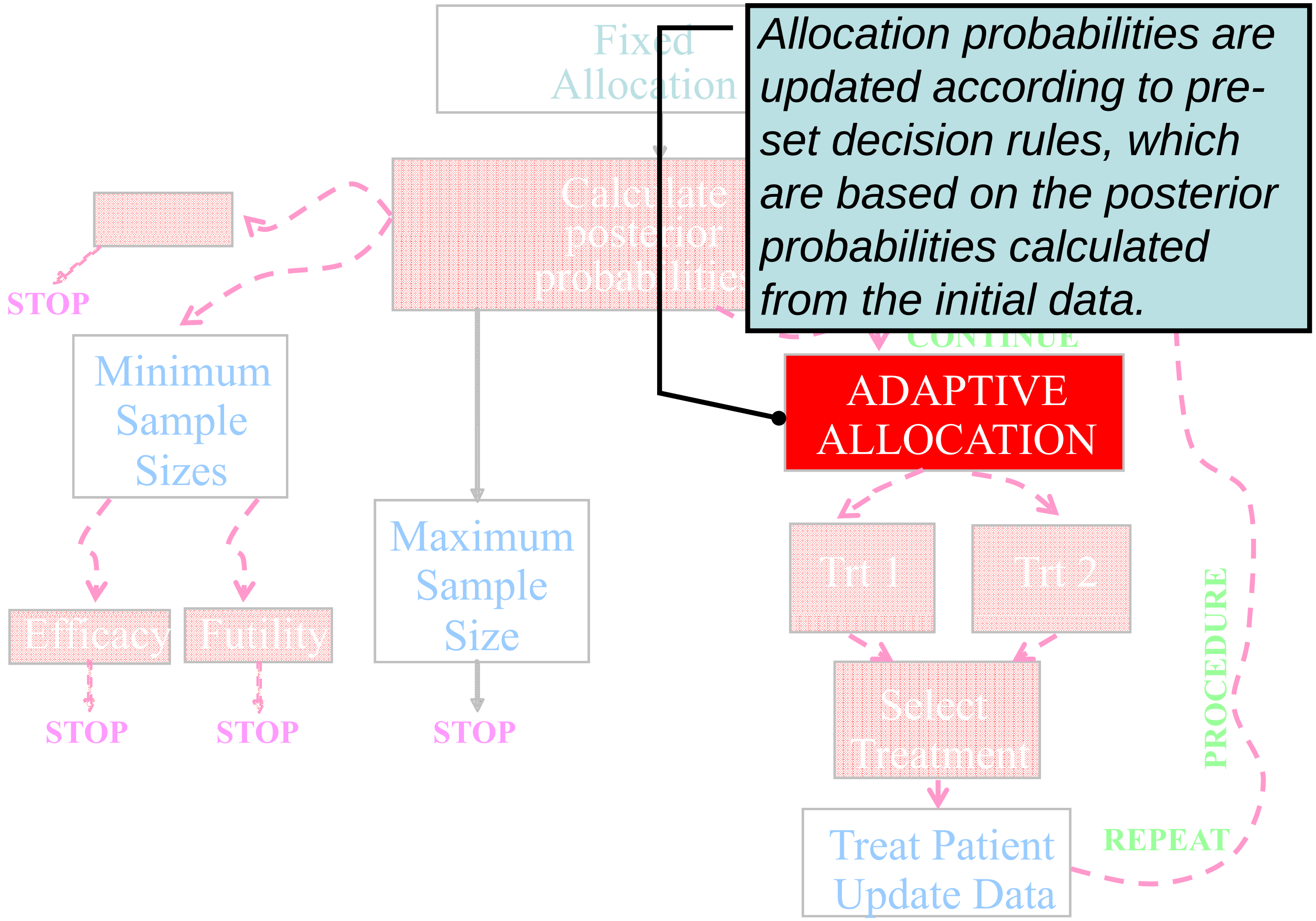
Effects of Measurement Error



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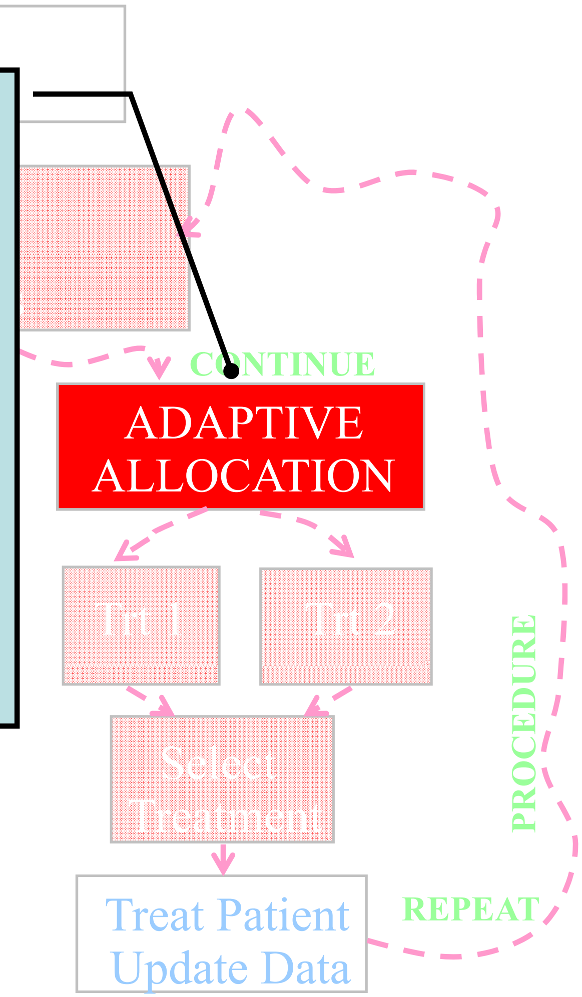
$P\left(\tilde{y}_j^* = 1 \mid \tilde{\mathbf{y}}, \boldsymbol{\alpha}, \boldsymbol{\beta}, \tau_u, \tau_x\right)$

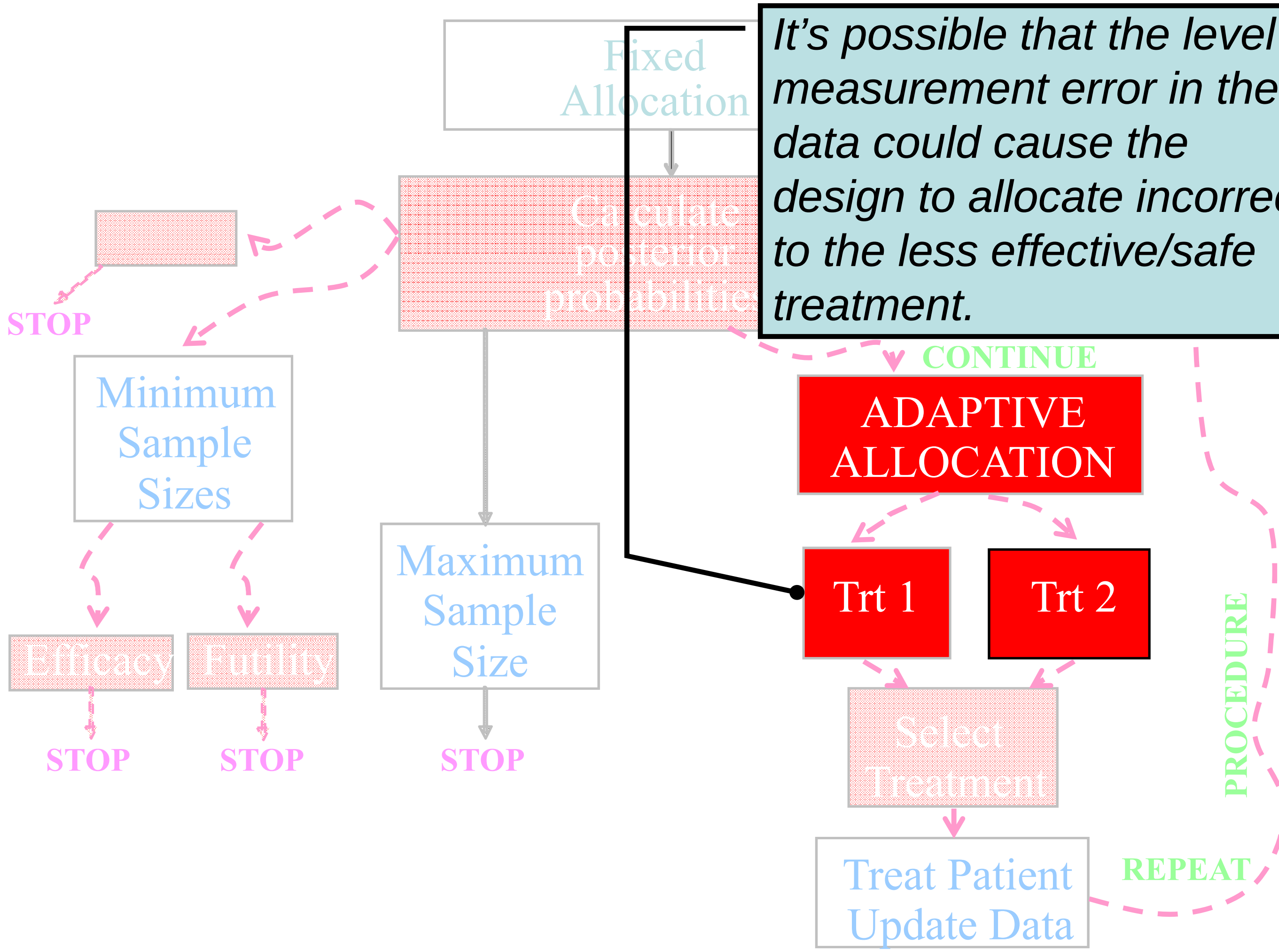
Effects of Measurement Error

Allocation probabilities are determined by the posterior predictive probability of response for the next patient that enters the trial.

$$P\left(T_j\right) = \frac{P\left(\tilde{y}_j \mid \tilde{\mathbf{y}}, \boldsymbol{\beta}, \tau_u, \tau_x\right)}{\sum_j P\left(\tilde{y}_j \mid \tilde{\mathbf{y}}, \boldsymbol{\beta}, \tau_u, \tau_x\right)}$$

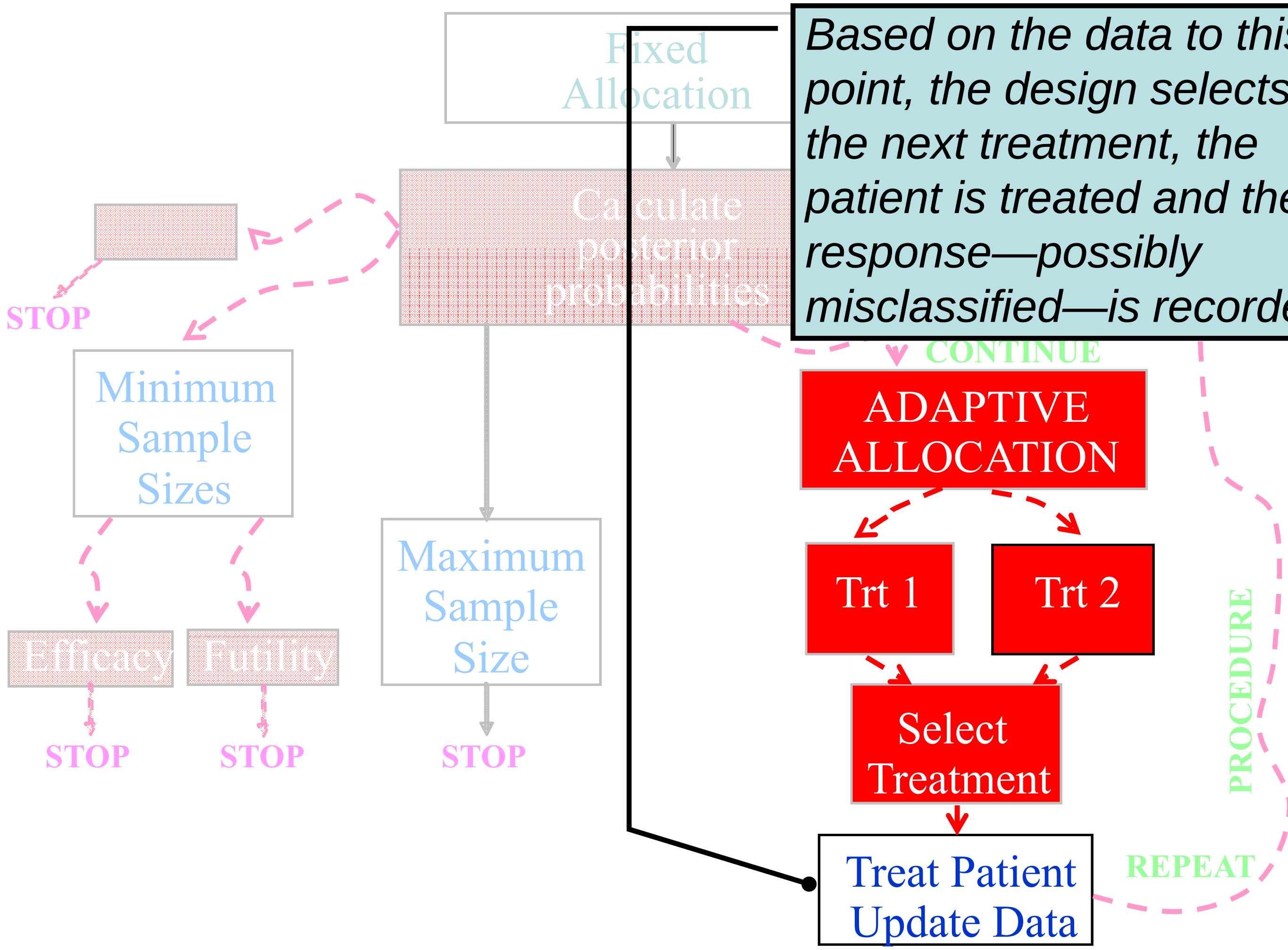


Effects of Measurement Error



It's possible that the level of measurement error in the data could cause the design to allocate incorrectly to the less effective/safe treatment.

Effects of Measurement Error



Based on the data to this point, the design selects the next treatment, the patient is treated and their response—possibly misclassified—is recorded.

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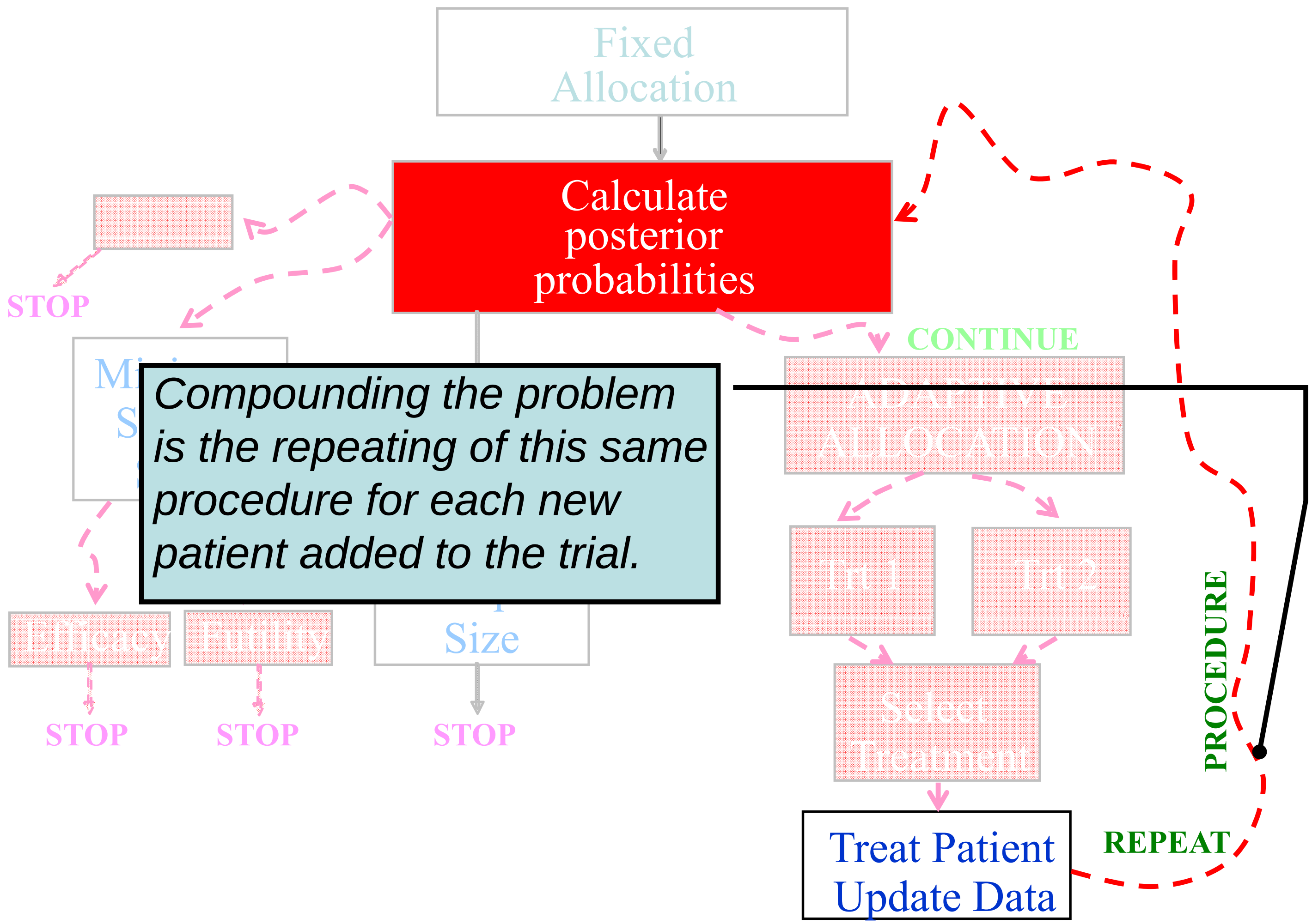
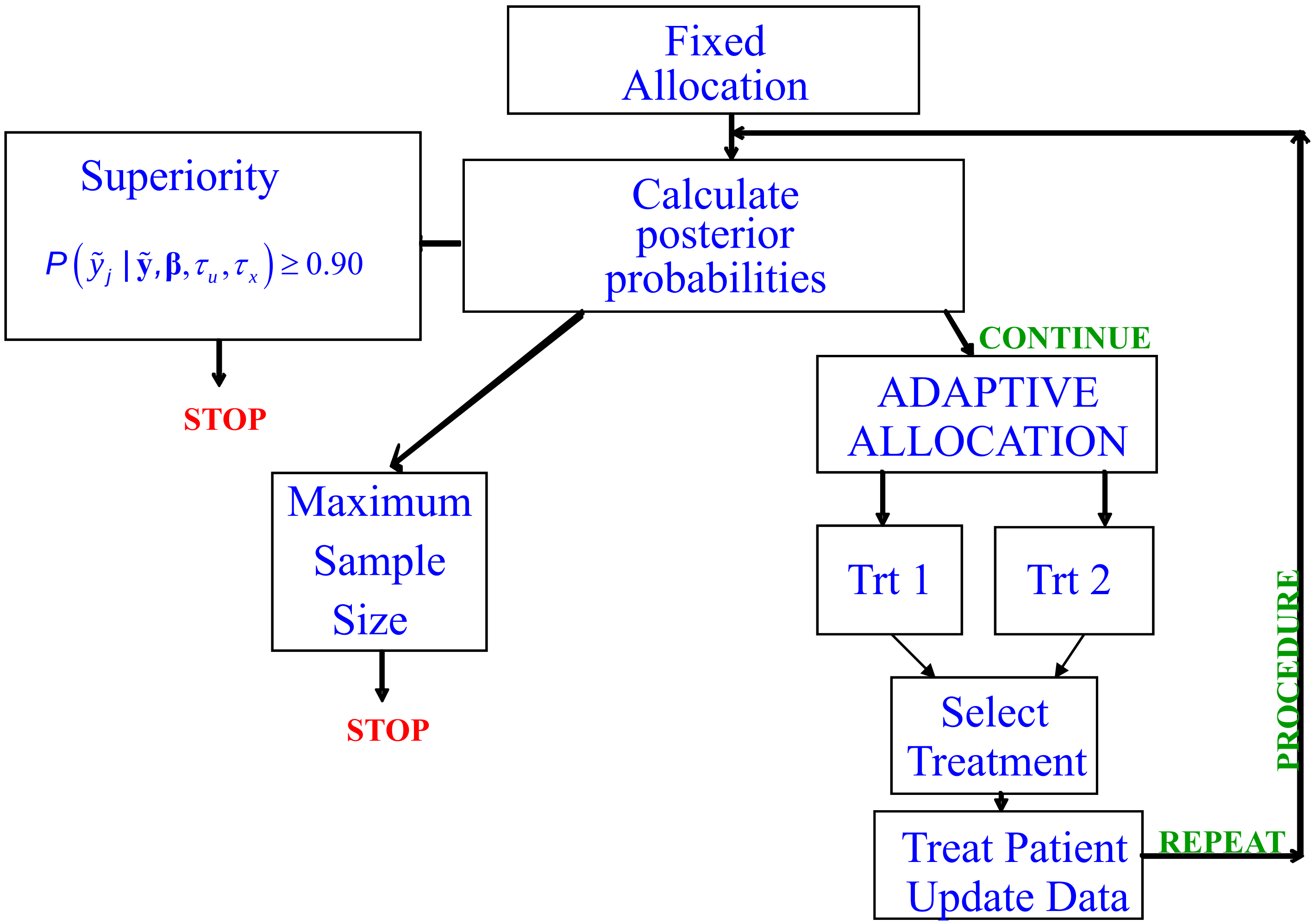
Effects of Measurement Error



Compounding the problem is the repeating of this same procedure for each new patient added to the trial.

A Simplified Bayesian Adaptive Design



Examples Illustrating Performance under Measurement Error

- Scenarios motivated by the coronary heart disease example
- Patient's SBP is given by the surrogate variable, w_i
- Patient's true SBP, x_i, ranges between 90 and 130, using ln(SBP−50).

	Scenario	
Parameter	I	II
β_0	−6.5	−6.5
β_1	1.5	1.3
β_2	0.4	0.4
μ	4.0	4.0

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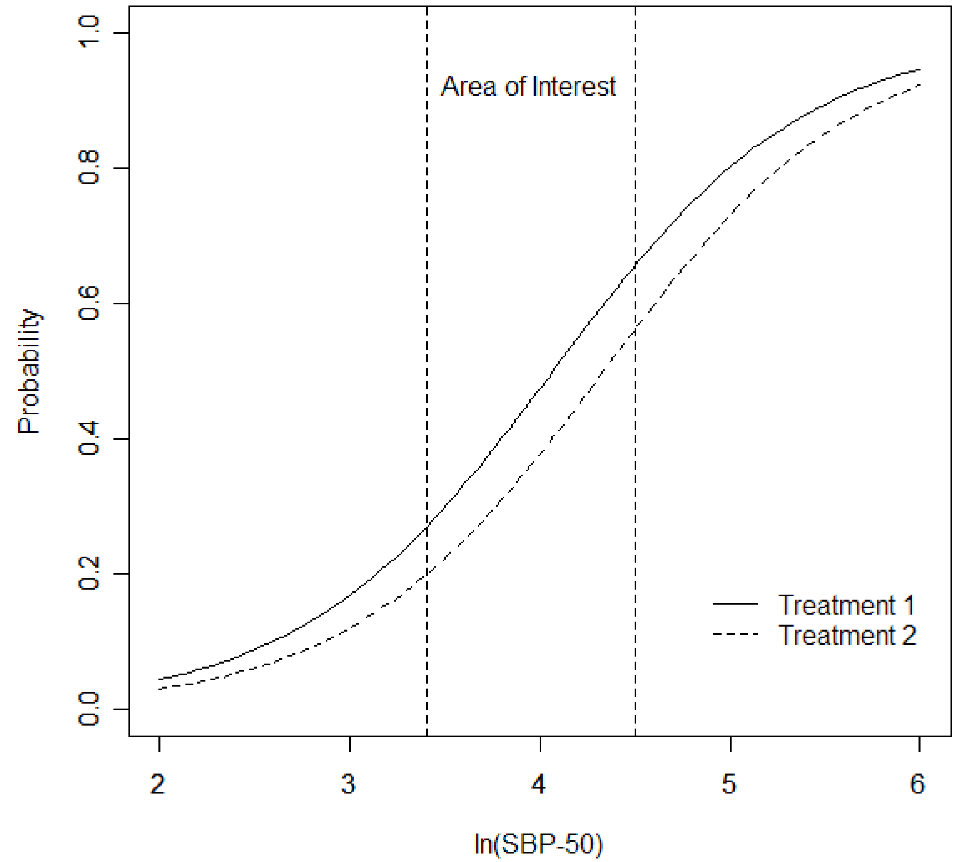
Treatment Effect

- The treatment effect, β_2, is a parameter of interest in both patient allocation probabilities and stopping points in the adaptive design scheme.



Model Check

- Every patient entering the trial during the adaptive phase requires the computation of a posterior predictive probability based on data accrued to that point.

- For each entering patient, posterior and posterior predictive distributions must be constructed. This is done using MCMC methods:

- MCMC specifications:
  - 2 chains
  - 60,000 iterations
  - Burn-in of 1,000
  - Thinning of 10

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Scenario I

- We place normal priors on the regression coefficients β_0, β_1, and $\beta_{2.}$

- To emulate an informative prior, we place a Gamma (25, 1) prior on τ_x since the mean of that distribution corresponds to the "true" value of $\tau_x = 25$ used to generate the data.

- Although we used $\tau_u = \tau_x$ in our data generation, suppose we believe that τ_u is slightly smaller than τ_x . In that case, we might place a Beta (12, 1) prior on ϕ, for $\tau_u = \phi\tau_x$.

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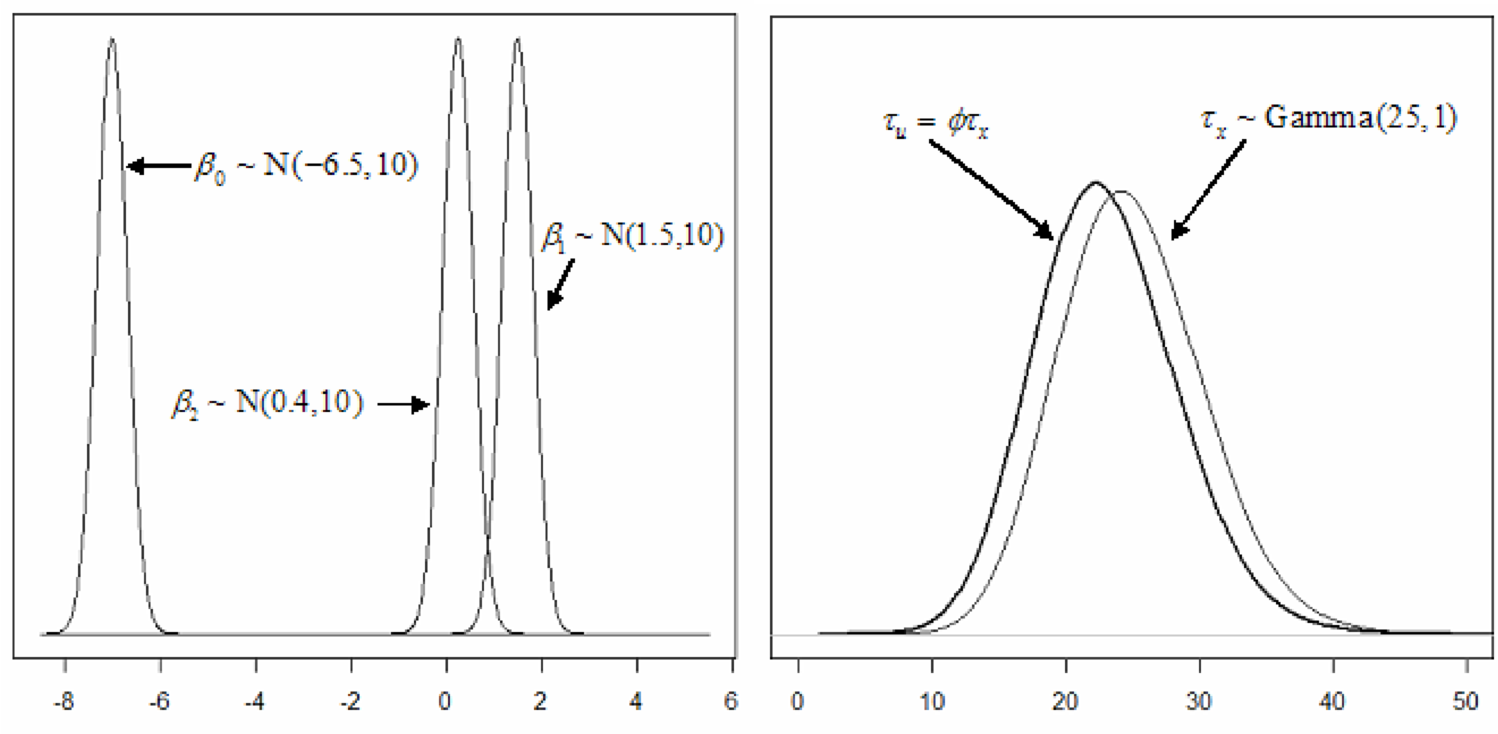
Priors for Scenario I



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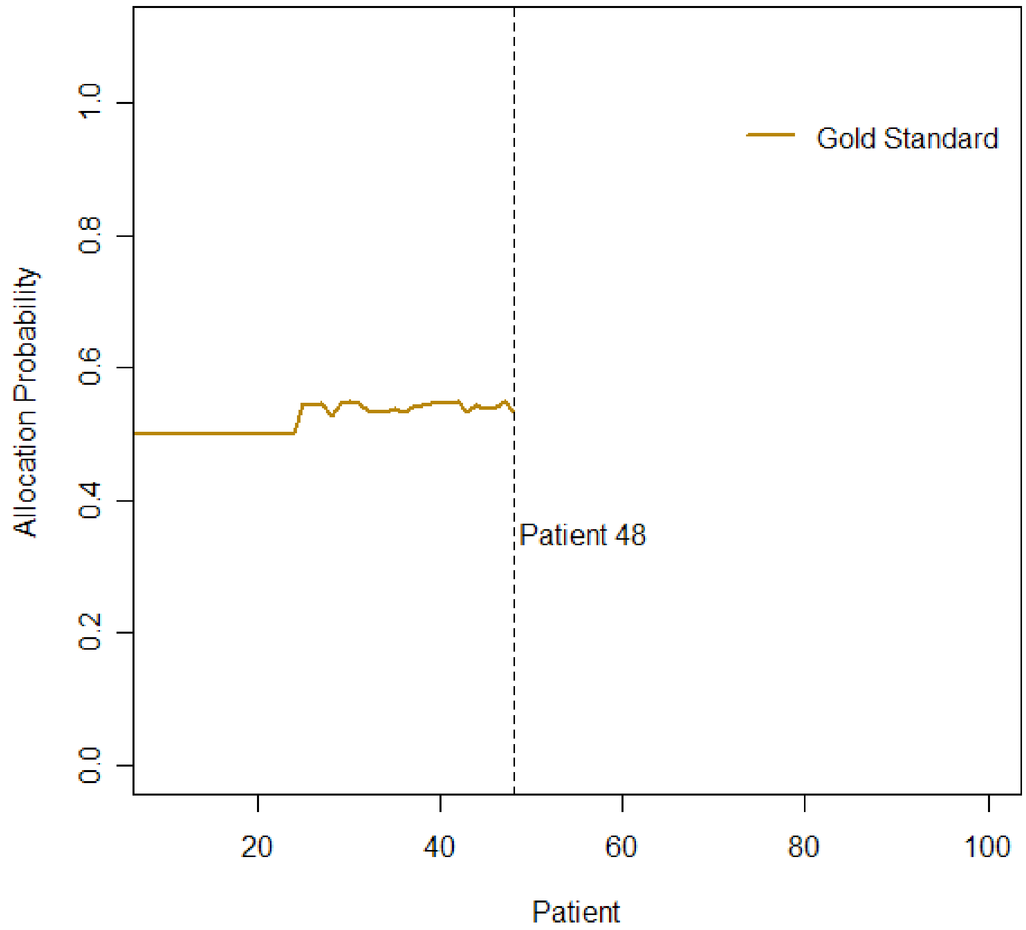
Results: Scenario I



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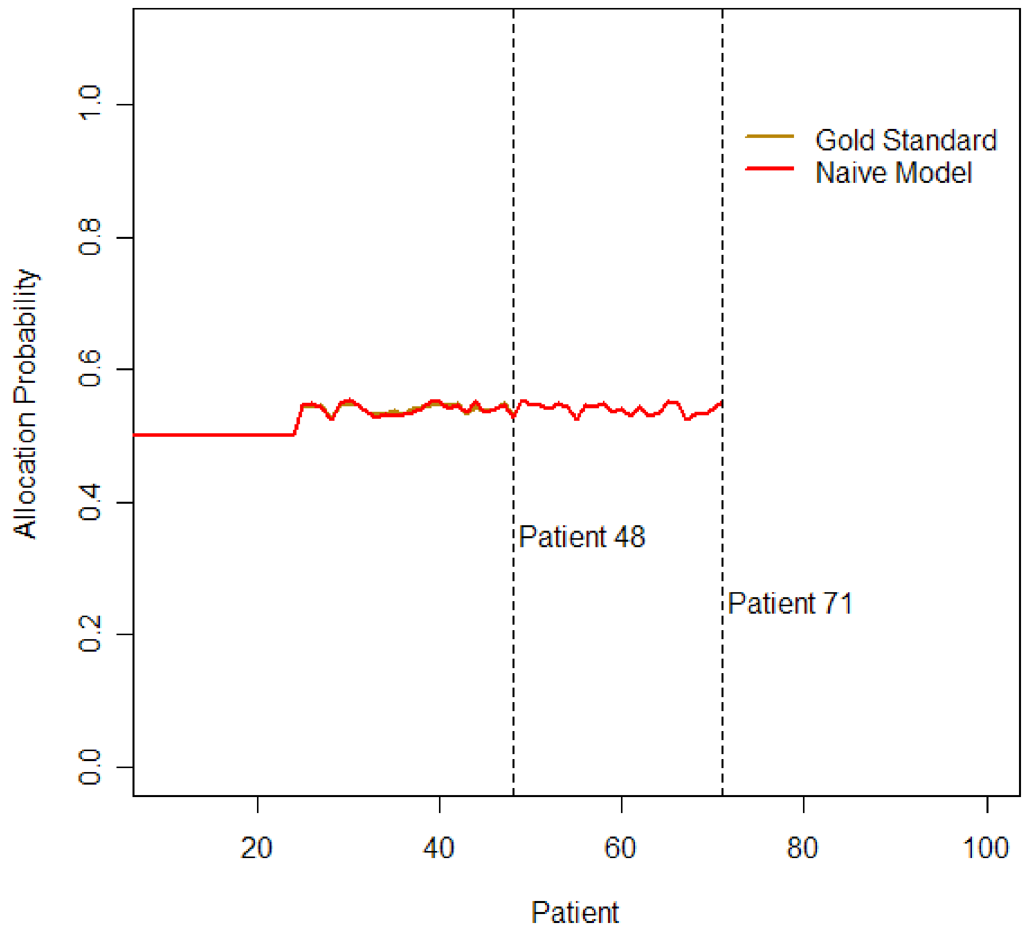
Results: Scenario I



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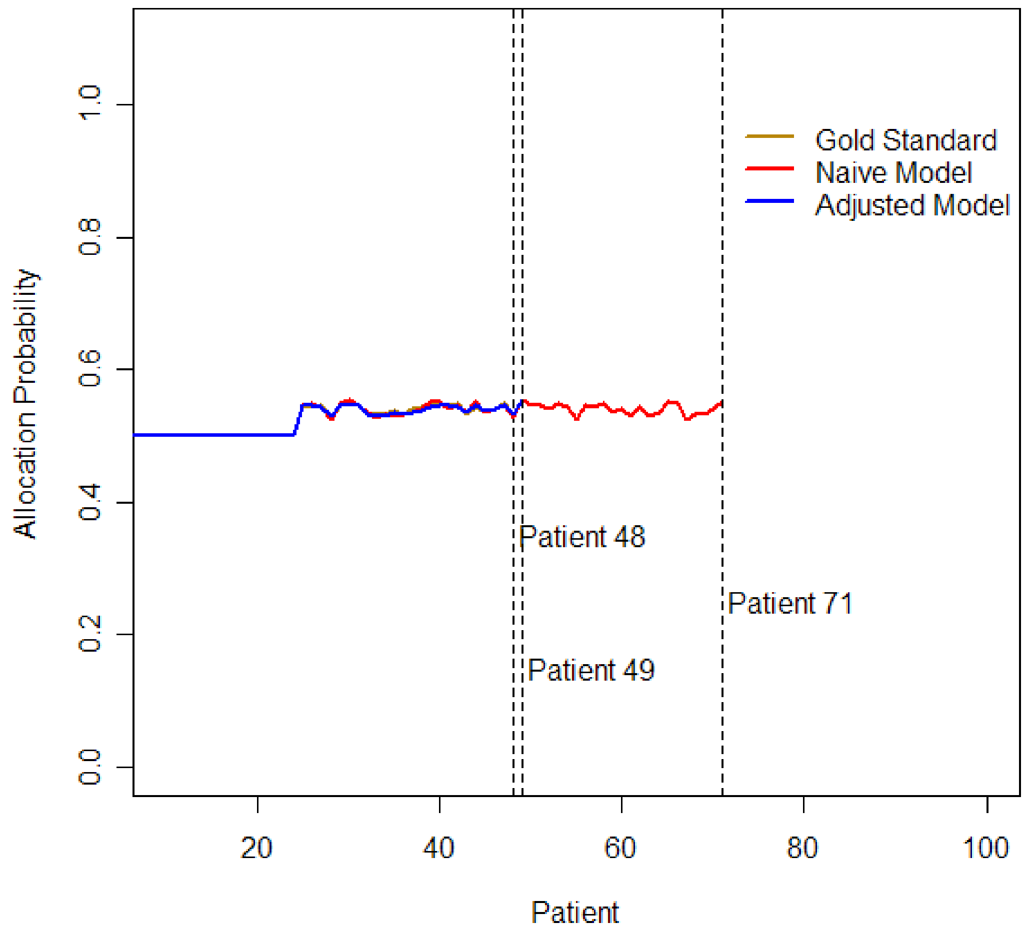
Results: Scenario I



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Results: Scenario I

Results	Model		
	Gold Standard	Naïve	Adjusted
Patient Stopping Point	48	71	49
Final Allocation Probability for T_1	53%	56%	55%
Number of Patients Assigned to T_2	10	26	11

Scenario II

- We use $\tau_u = 11$ and $\tau_x = 25$ in this example
- Prior structures for the regression coefficients are as in Scenario I
- Suppose again we believe τ_u is smaller than τ_x. To emulate an informative prior, we place a Gamma (25, 1) prior on τ_x since the mean of that distribution corresponds to the "true" value of $\tau_x = 25$ used to generate the data.
- In that case, we place a Beta (8, 8) prior on ϕ, for $\tau_u = \phi\tau_x$.

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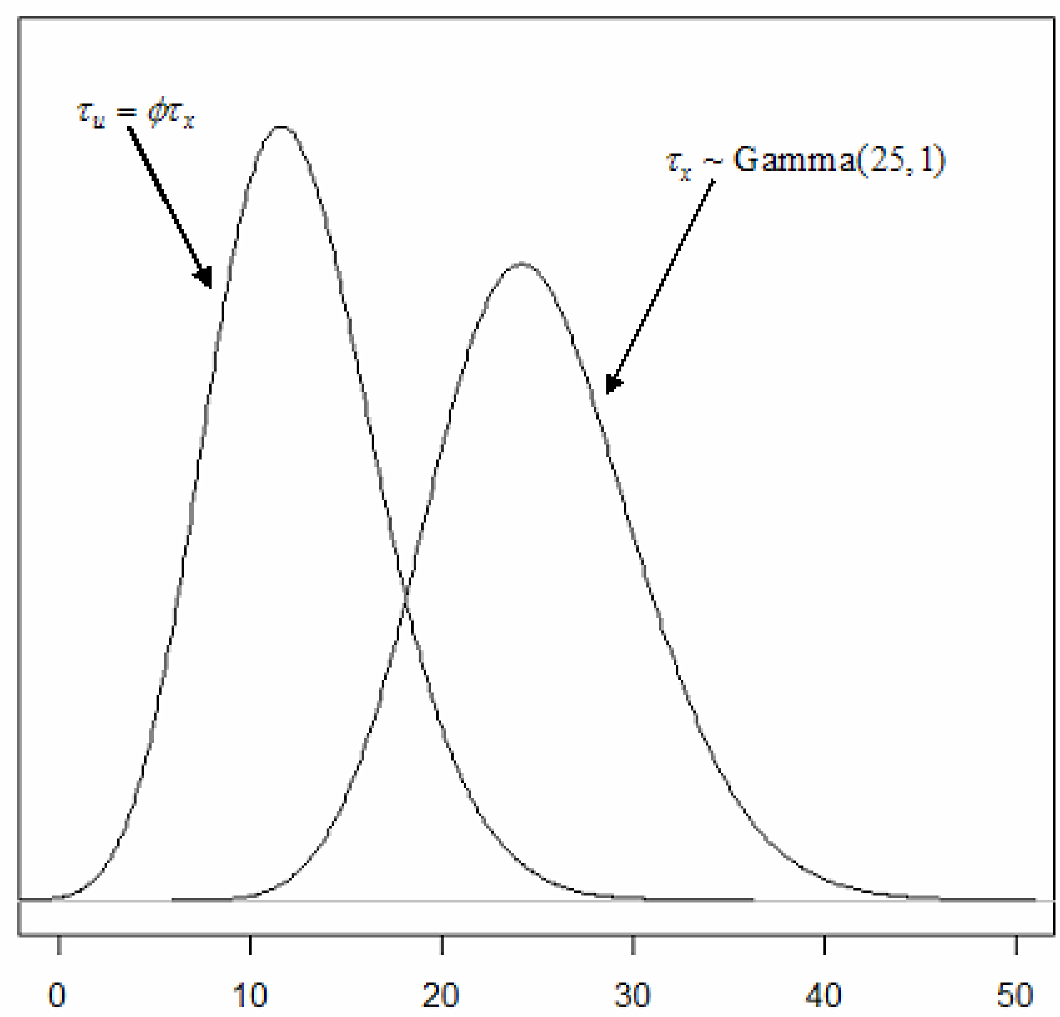
Priors for Precision: Scenario II



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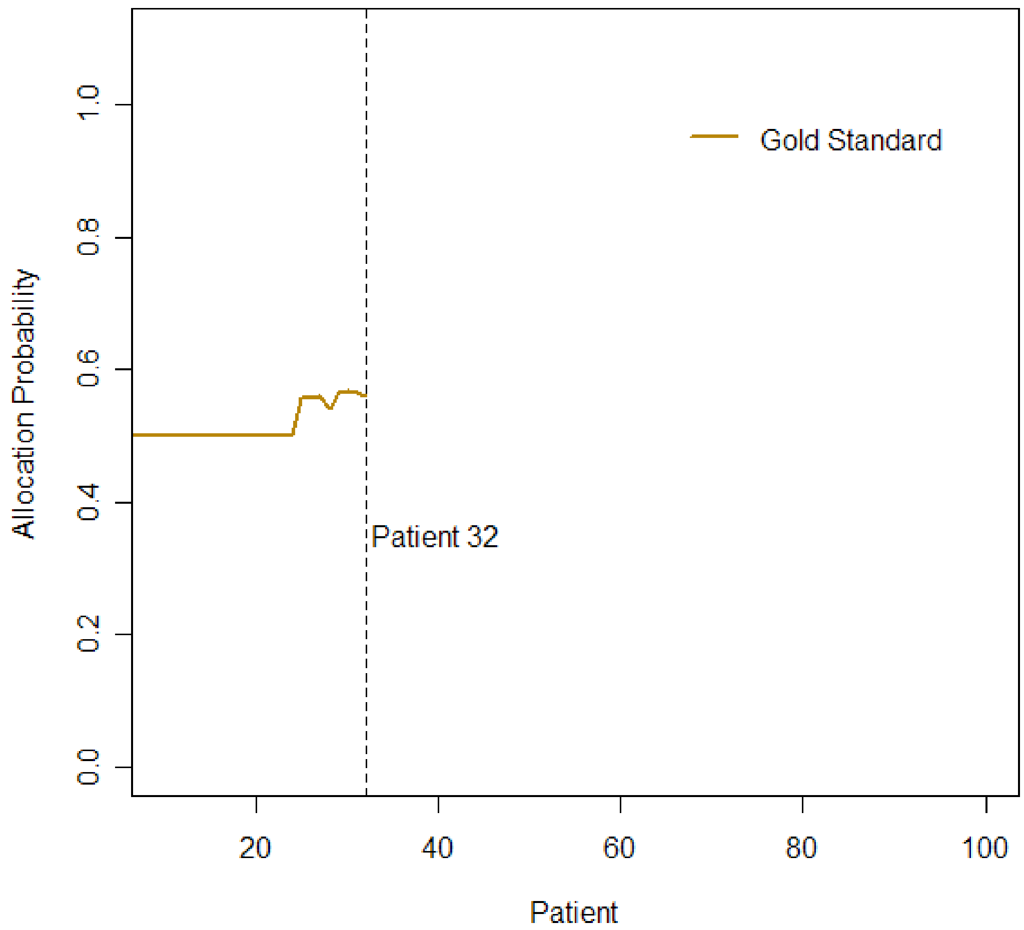
Results: Scenario II



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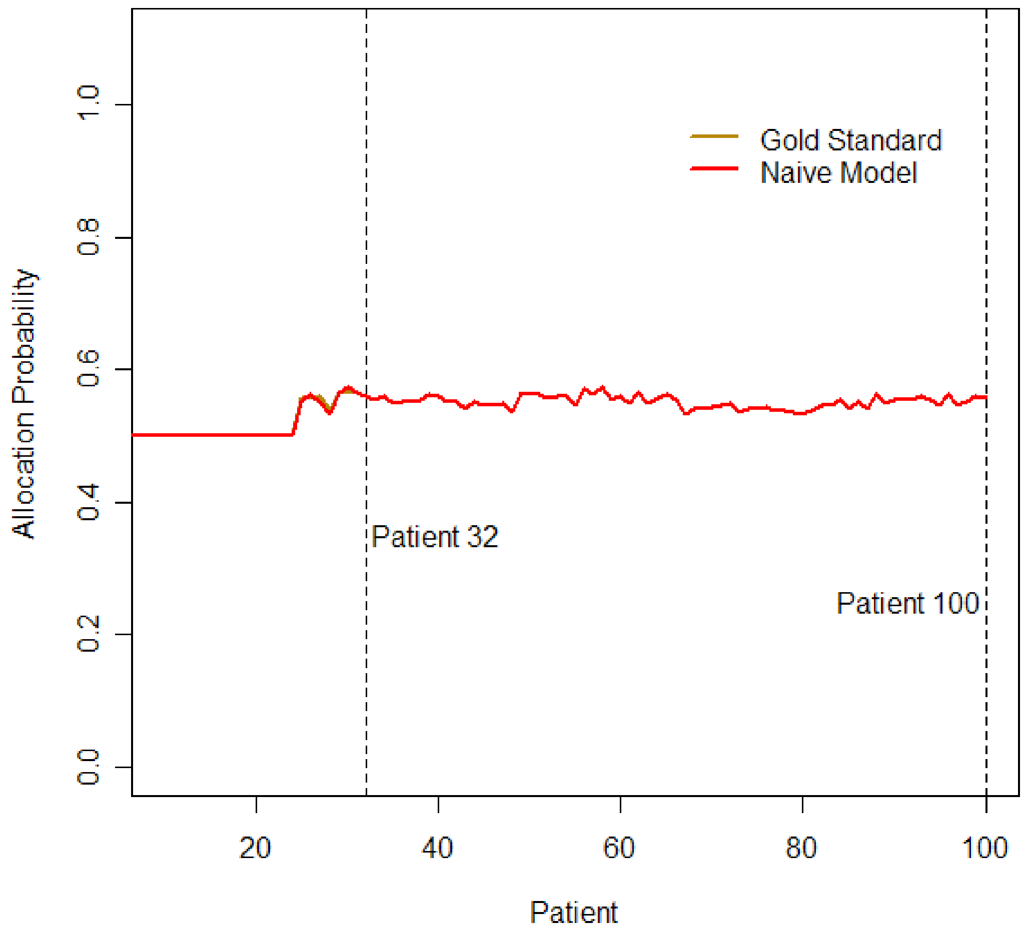
Results: Scenario II



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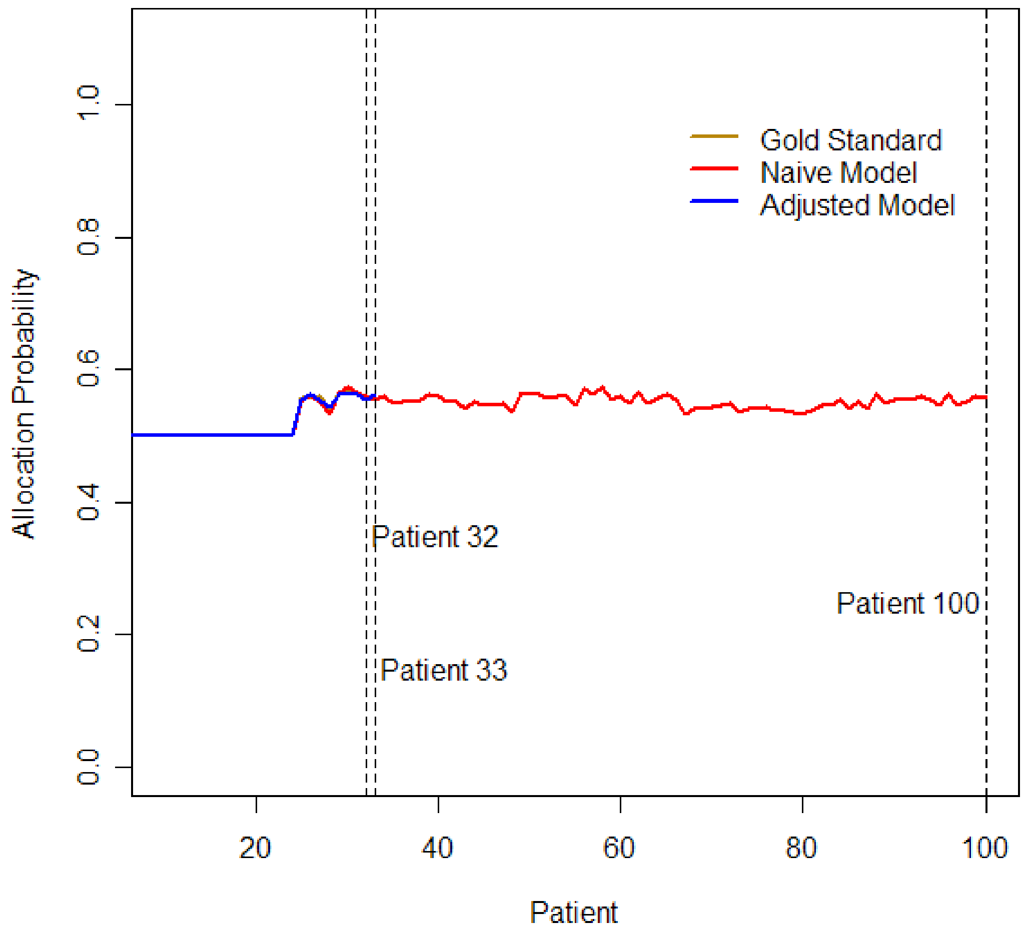
Results: Scenario II



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Results: Scenario II

	Model		
Results	Gold Standard	Naïve	Adjusted
Patient Stopping Point	32	100	33
Final Allocation Probability for T_1	56%	56%	56%
Number of Patients Assigned to T_2	3	40	4

Discussion

- The use of adaptive design methods in clinical trials is steadily increasing.
- These designs are efficient, ethical, and potentially require fewer patients to be enrolled into a trial.
- In clinical research, the ultimate goal of a clinical trial is to evaluate the effect of a test treatment compared to a control.
- However, the effect of a treatment can often be misleading due to measurement error.

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Future Research

- A study of the Berkson measurement error model.
- Further research could involve procedures for data where measurement error or misclassification is differential.
- Perform simulation studies that correspond to the scenarios illustrated today.
- What other factors play a role in the level of disturbance measurement error inflicts on the design, and to what extent (e.g., decisions driving the allocation, initial allocation probabilities, treatment similarities and differences, initial sample size)?

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References

Armstrong, B. G. (1998), “Effect of measurement error on epidemiological and occupational exposures,” *Occupational and Environmental Medicine*, 55, 651-656.

Bekele, B. N. and Shen, Y. (2005), “A Bayesian approach to jointly modeling toxicity and biomarker expression in a phase I/II dose-finding trials,” *Biometrics*, 61, 343-354.

Berkson, J. (1950), “Are there two regressions?” *Journal of the American Statistical Association*, 45, 164-180.

Berry, D. A. (2004), “Bayesian statistics and the efficacy and ethics of clinical trials,” *Statistical Science*, 19, 175-187.

Berry, D. A., Mueller, P., Grieve, A. P., Smith, M., Parke, T., Blazek, R., Mitchard, N., and Krams, M. (2000), *Adaptive Bayesian Designs to Dose-Ranging Drug Trials*, vol. 5 of *Case Studies in Bayesian Statistics*, New York: Springer.

Bross, I. (1954), “Misclassification in 2x2 tables,” *Biometrics*, 10, 378-486.

Carroll, R. J., Ruppert, D., Stefanski, L. A., and Crainiceanu, C. M. (2006), *Measurement Error in Nonlinear Models: A Modern Perspective*, Boca Raton: Chapman and Hall/CRC, 2nd ed.

Carroll, R. J., Wang, S., and Wang, C. Y. (1995), “Prospective analysis of logistic case-control studies,” *Journal of the American Statistical Association*, 90, 157-169.

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References

Case, L. D., Kimmick, G., Paskett, E. D., Lohman, K., and Tucker, R. (2002), “Interpreting measures of treatment effect in cancer clinical trials,” *The Oncologist*, 7, 181{187.

Chang, M. (2008), *Adaptive Design Theory and Implementation Using SAS and R*, Boca Raton: Chapman and Hall/CRC.

Chow, S.-C. and Chang, M. (2005), “A hybrid Bayesian adaptive design for dose response trials,” *Journal of Biopharmaceutical Statistics*, 15, 677-691.

---- (2007), *Adaptive Design Methods in Clinical Trials*, Boca Raton: Chapman and Hall/CRC.

Cui, L., Hung, H. M. J., and Wang, S. J. (1999), “Modification of sample size in

group sequential trials,” *Biometrics*, 55, 651-660.

EMEA (2002), *Point to Consider on Methodological Issues in Confirmatory Clinical Trials with Flexible Design and Analysis Plan*, The European Agency for the Evaluation of Medicinal Products Evaluation of Medicines for Human Use. CPMP/EWP/2459/02, London, UK.

Gallo, P., Chuang-Stein, C., Dragalin, V., Gaydos, B., Krams, M., and Pinheiro, J. (2006), \Adaptive design in clinical drug development - An executive summary of the PhRMA Working Group (with discussion)," *Journal Biopharmaceutical Statistics*, 16, 275-283.

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References

Gelman, A., Carlin, J. B., Stern, H. S., and Rubin, D. B. (2004), *Bayesian Data Analysis*, Chapman and Hall/CRC, 2nd ed.

Giles, F. J., Kantarjian, H. M., Cortes, J. E., Garcia-Manero, C., Verstovsek, S., Faderl, S., Thomas, D. A., Ferrajoli, A., O'Brien, S., Wathen, J. K., Xiao, L.-C., Berry, D. A., and Estey, E. H. (2003), "Adaptive Randomized Study of Idarubicin and Cytarabine Versus Troxacitabine and Cytarbine Versus Troxacitabine and Idarubicin in Untreated Patients 50 Years or Older With Adverse Karyotype Acute Myeloid Leukemia," *Journal of Clinical Oncology*, 21, 1722-1727.

Gustafson, P. (2004), *Measurement Error and Misclassification in Statistics and Epidemiology: Impacts and Bayesian Adjustments*, Boca Raton: Chapman and Hall/CRC.

Gustafson, P., Le, N., and Saskin, R. (2001), "Case-control analysis with partial knowledge of exposure misclassification probabilities," *Biometrics*, 57, 598-609.

Kannel, W. B., Neaton, J. D., Wentworth, D., Thomas, H. E., Stamler, J., Hulley, S. B., and Kjelsberg, M. O. (1986), "Overall and coronary heart disease mortality rates in relation to major risk factors in 325,348 men screened for MRFIT," *American Heart Journal*, 112, 825-836.

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References

Krams, M., Lees, K. R., Hacke, W., Grieve, A. P., Orgogozo, J.-M., and Ford, G. A. (2003), "Acute Stroke Therapy by Inhibition of Neutrophils (ASTIN): An Adaptive Dose-Response Study of UK-279,276 in Acute Ischemic Stroke," *Stroke*, 34, 2543-2548.

Maca, J., Bhattacharya, S., Dragalin, V., Gallo, P., and Krams, M. (2006), "Adaptive seamless phase II/III designs - Background, operational aspects, and examples," *Drug Information Journal*.

Nadarajah, S. and Gupta, A. (2004), *Handbook of Beta Distributions and Its Applications*, New York: Chapman and Hall/CRC.

Prescott, G. J. and Garthwaite, P. H. (2002), "A simple Bayesian analysis of misclassified binary data with a validation study," *Biometrics*, 58, 454-458.

---- (2005), "A Bayesian approach to prospective binary outcome studies with misclassification in a binary risk factor," *Statistics in Medicine*, 24, 3463-3477.

Spann, M. (2006), "Bayesian Adaptive Designs for Non-Inferiority and Dose Selection Trials," Ph.D. thesis, Baylor University.

Thall, P. F. and Russell, K. E. (1998), "A strategy for dose-finding and safety monitoring based on efficacy and adverse outcomes in phase I/II clinical trials," *Biometrics*, 54, 251-264.

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