Bayesian Monitoring of A Longitudinal Clinical Trial Using R2WinBUGS

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Outline

- Review of WinBUGS and R2WinBUGS
- Decision Problem in Early Drug Development
- An Algorithm to Use Totality of Data
  - Use only patients who have completed final assessment
  - Imputation of incomplete data at an interim stage
  - Use a longitudinal model with a dose-response (DR) model
- Evaluation of Probability of Success for Decision-Making
  - DR modeling using Normal Dynamic Linear Model (NDLM)
- Summary

WinBUGS

- WinBUGS (**B**ayesian inference **U**sing **G**ibbs **S**ampling) is a software for Bayesian analysis of complex statistical models using Markov chain Monte Carlo (MCMC) methods.

- Implementation of Bayesian model using WinBUGS
  - Difficult to get nice graphical or text output for results reporting
  - Need to run the BUGS code several times in the analysis of clinical trials data – especially in monitoring of clinical trials
  - Need to have the capability to run a BUGS program by calling WinBUGS from R through **R2WinBUGS**

R2WinBUGS

- An R package originally written by Andrew Gelman.
- Calls WinBUGS through R, summarizes inference and convergence in table and graph, and saves simulation results (sims.array or sims.matrix) for easy access in R.
- The results can be used for further analyses by the facilities of the coda (Output Analysis and Diagnostics for MCMC) and boa (Bayesian Output Analysis Program for MCMC) packages.
- Same computational advantages of WinBUGS with statistical and graphical capabilities of R.

How R2WinBUGS works?

- Make model file
  - Model file must contain WinBUGS syntax.
  - Can either be written in advance or by R itself through the write.model( ) function.
- Initialize
  - Both data and initial values are stored as lists.
  - Create parameter vector with names of parameters to be tracked.
- Run
  - bugs( ) function
  - Extract results from sims.array or sims.matrix, which contain MCMC simulated posterior distribution for each parameter.

Decision Problem in Early Drug Development

- First (proof of concept [POC] or early dose-ranging) study is designed based on preclinical data
  - Study is designed at best with “guesstimate” of treatment effect
- At the end of POC/early dose-ranging trial, efficacy and safety information is available on a small number of patients
  - Significance testing is not useful (too little data!)
- The key question: Should we continue development, terminate the project, or put it on hold?

Traditional Approach to Early Drug Development

- Design POC study with little or no knowledge of effect size
  - Sample size chosen to demonstrate difference vs. placebo
  - May not include active control
  - If active control included, probably underpowered

- Ignore the Target Product Profile (TPP)
  - Does the drug work? vs. Will the drug achieve both regulatory and commercial needs?

Alternative Approach to Early Drug Development

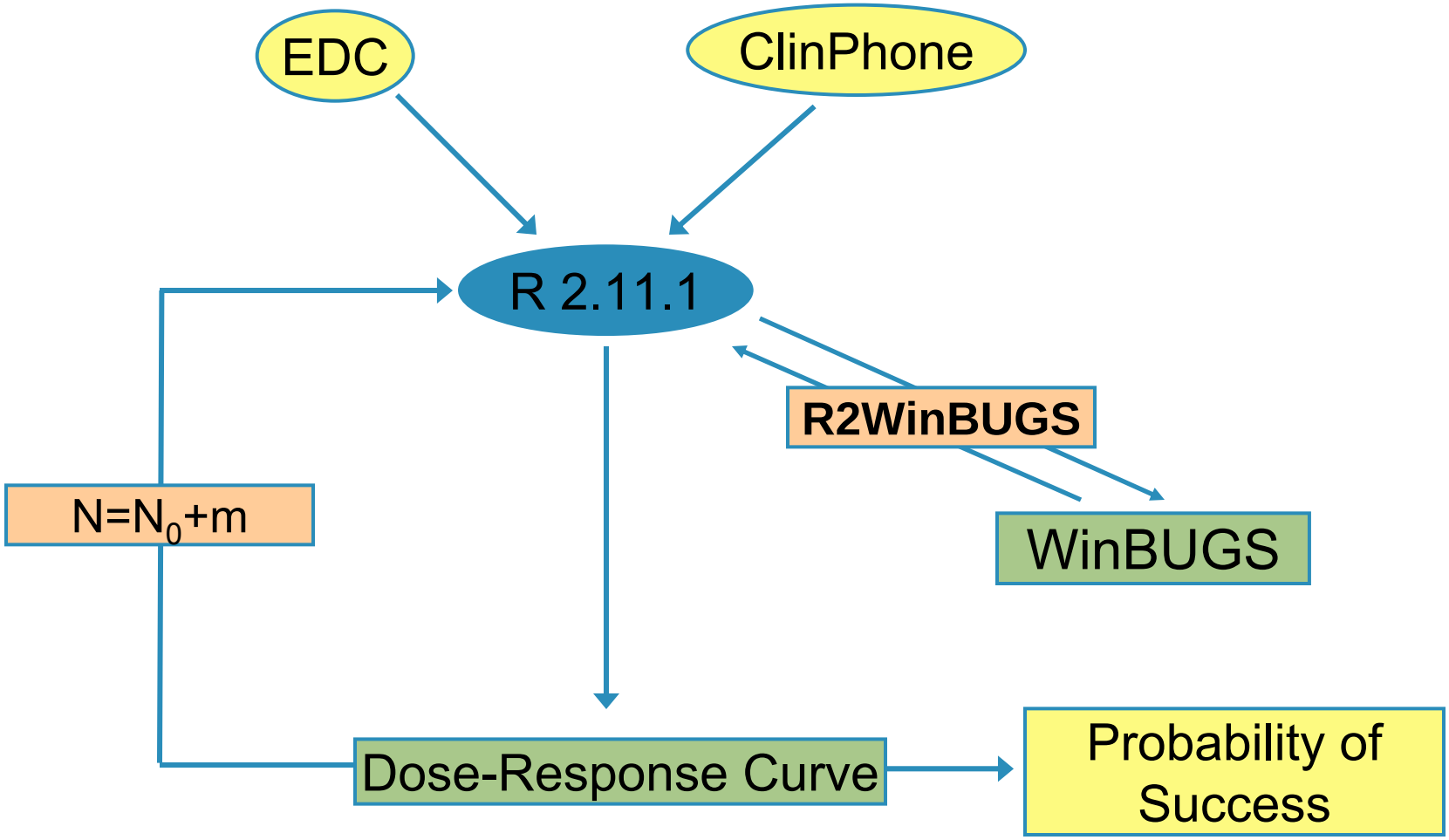
- Continuously update estimate of treatment effect
  - More interim analyses may improve efficiency
- Assess whether compound will meet TPP
  - Use all data available from POC study and other sources to update the probability of achieving TPP
- Use modeling and simulations to predict results of ongoing or future trials
- Bayesian approach using transparent assumptions subject to discussion and ratification

Alternative Approach

- Exploit totality of accumulated data/knowledge in a Bayesian framework and evaluate the probability of success for a drug candidate in meeting TPP.

- Develop an algorithm that provides
  - An estimate of probability of success at an interim stage to plan for further development or an opportunity to stop the study for futility
  - An estimate of probability of success in a phase III study if the study is not stopped early for futility

An Algorithm using R and WinBUGS



Case Study

- Patient population: Patients diagnosed with mild-to-moderate Alzheimer's disease
- Treatment period: 12 weeks
- Assessments at Baseline (BL), Weeks 4, 8 and 12, labeled as Y_1, Y_4, Y_8, and Y_{12}.
- Treatment arms: Placebo and 6 doses of the experimental add-on drug, 5 mg, 10 mg, 15 mg, 20 mg, 30 mg and 35 mg.
- Doses are labeled as d =1 (Placebo), 2, 3, 4, 5, 6 and 7.
- Primary endpoint: Change from baseline in Alzheimer's disease assessment scale-cognitive subscale (ADAS-Cog) total score after 12 weeks of treatment. A negative change is considered beneficial.
- A normal dynamic linear model (NDLM) is used to characterize DR curve for the primary endpoint.

Analysis Options

- Interim Analysis
  - Only limited data available for DR modeling
    - Use all the data available on all patients with at least one post-BL assessment.
      - Impute yet to be observed data using a longitudinal model (very complex when integrated with a DR Model).
  - DR Model (with or without a longitudinal model) can be implemented in R using WinBUGS through R2WinBUGS.
  - In an alternate setting, interim analysis includes only patients who have completed final assessment.
- At the end of the study (only when study is not stopped early for futility)
  - Complete data is available for evaluating dose-response.
  - DR model can be implemented as in the interim analysis case.
  - Estimate probability of success in Phase III using all prior data and current study data.

Imputation of Incomplete Data at An Interim Stage

- When interim analyses are conducted, some subjects have complete data, but others have incomplete or partial information.
- A simple regression model is used to impute the value of Y_{12} given the last observed values of Y_1, Y_4, Y_8, or Y_1, Y_4 .
- Let $Y_{t,i}^{d}$ be the ADAS-Cog score at time point t for subject i on dose d.
  - Given Y_1, Y_4 and Y_8,

$$Y_{12,i}^{d} \mid Y_{1,i}^{d}, Y_{4,i}^{d}, Y_{8,i}^{d} \sim N(b_{0d} + b_{1d} Y_{1,i}^{d} + b_{4d} Y_{4,i}^{d} + b_{8d} Y_{8,i}^{d}, \sigma^2)$$

  - Given Y_1 and Y_4,

$$Y_{12,i}^{d} \mid Y_{1,i}^{d}, Y_{4,i}^{d} \sim N(b_{0d} + b_{1d} Y_{1,i}^{d} + b_{4d} Y_{4,i}^{d}, \sigma^2)$$

  - Non-informative prior on b_{0d}, b_{1d}, b_{4d}, b_{8d} and σ^2,

$$b_{jd} \sim N(0, 1000) \text{ for } j = 0, 1, 4, 8$$

$$\sigma^2 \sim Inverse\,Gamma(0.01, 1000)$$

NDLM

For subject *i* on dose *d,*

- Observation equation:

$$Y_{12,i}^{d} - Y_{1,i}^{d} \sim N(\theta_d, \sigma^2)$$

$$\sigma^2 \sim Inverse\,Gamma(0.001, 1000)$$

Vague prior on sampling precision

- Evolution (system) equation:

$$\theta_d \sim N(\theta_{d-1}, \tau^2)$$

$$\theta_1 \sim N(0, \tau^2)$$

Prior on dose response of Placebo

where the drift factor τ is assumed to be 0.5. The larger the τ, the less constraint of relationship between neighboring doses.

Criteria for Success and Failure

Success if $P[(\theta_{d^*} - \theta_1) \geq 1.75] \geq 0.80$ for some dose d*

CSD1: $(\theta_{d^*} - \theta_1) \geq 1.75$

Futility if $P[(\theta_d - \theta_1) \leq 1.38] \geq 0.95$ for all doses d

CSD2: $(\theta_d - \theta_1) \leq 1.38$

BUGS Code for fitting NDLM for DR

```
model{
        for (j in 1:J) {
                y[j]  ~ dnorm(mu[j], sigma2inv)
                mu[j] <- theta[dose[j]]
        }
        for(k in 2:K) {
                theta[k]  ~ dnorm(mu.theta[k], 4)
                mu.theta[k] <- theta[k-1]
                effect[k] <- theta[k]-theta[1]
                p[k] <- step(theta[1]-theta[k]-1.38)
                p1[k] <- step(theta[1]-theta[k]-1.75)
        }
        theta[1]  ~ dnorm(0, 4)
        sigma2inv ~ dgamma(0.001, 0.001)
}
```

Number of patients

Observation equation

Number of doses

Evolution equation

Effect over placebo

Probability of futility at each dose

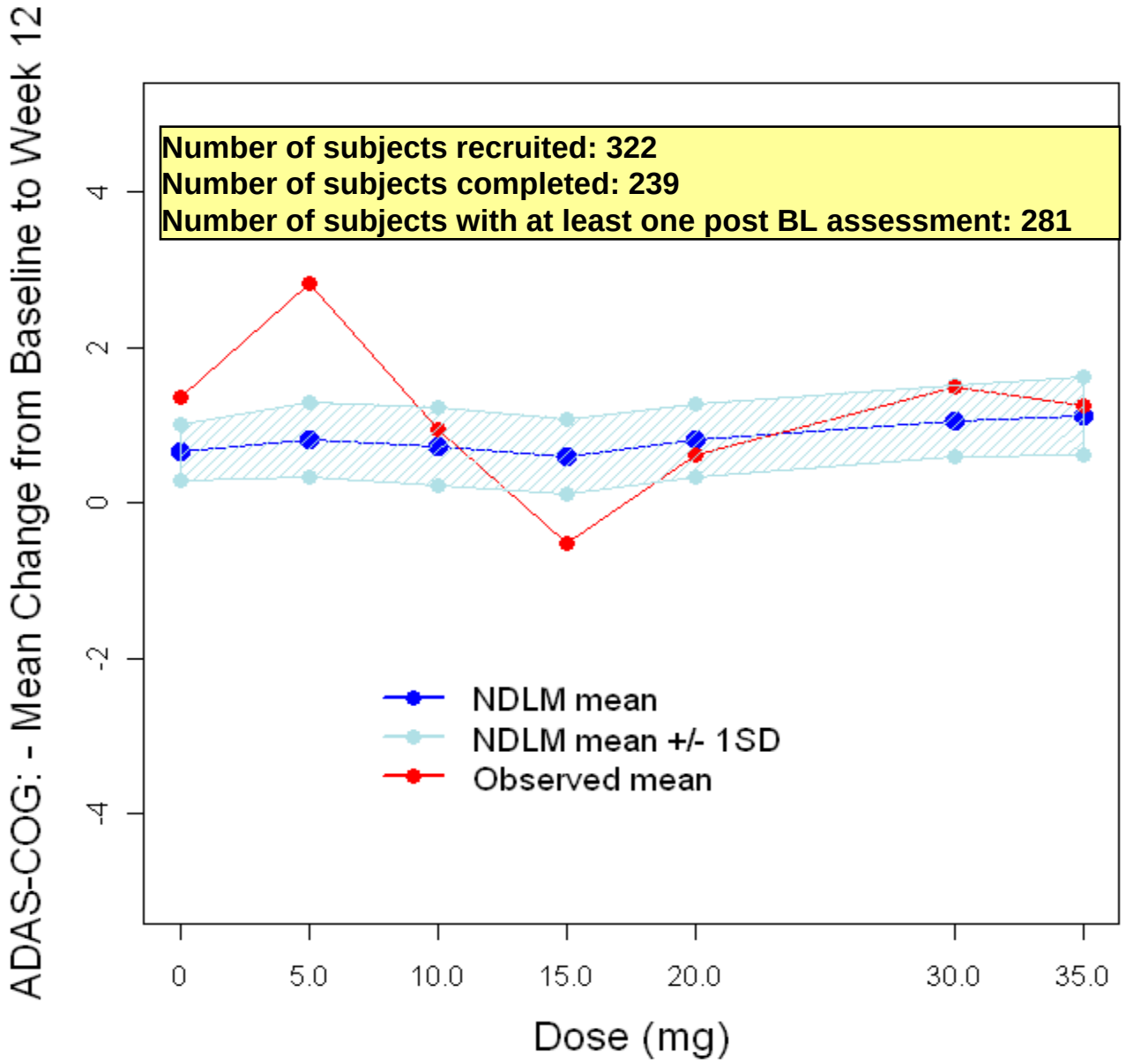
Probability of success at each dose

Prior dose response of Placebo

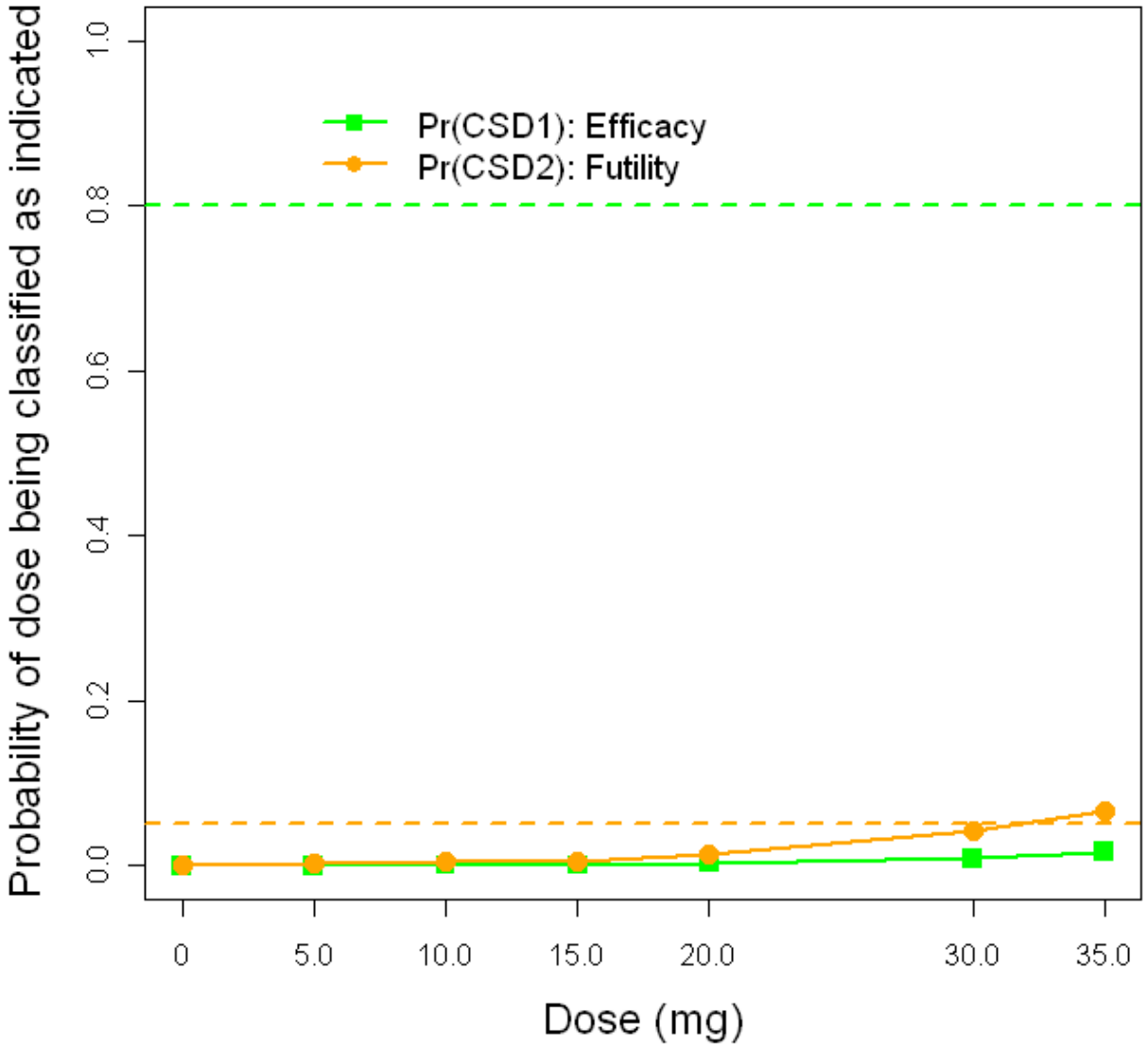
NOTE: WinBUGS uses precision in normal distn, precision=1/variance

Case 1 - Use Only Patients Who Had Completed Final Assessment

DR Curve – NDLM with N=239 Completers



Probability of Success
NDLM with N=239 Completers



Case 2 - Imputation of Incomplete Data at An Interim Stage

Observed data for 35 mg dose

subjid	trtcd	trtn	y1	y4	y8	y12
30111	F	7	15	20	19	14
30501	F	7	16	7	11	13
30509	F	7	26	22	24	17
30516	F	7	28	19	13	19
30601	F	7	36	32	30	31
30613	F	7	18	12	NA	NA
30614	F	7	8	NA	NA	NA
30901	F	7	13	14	8	5
31107	F	7	30	29	30	29
31204	F	7	13	20	14	15
31206	F	7	20	20	20	21
31208	F	7	16	12	15	11
31603	F	7	19	19	17	12
31701	F	7	21	12	9	4
31705	F	7	6	10	10	11
31809	F	7	27	30	29	NA
⋮						

Completer

Having Y_1, Y_4, Y_8

Having Y_1 and Y_4

Removed

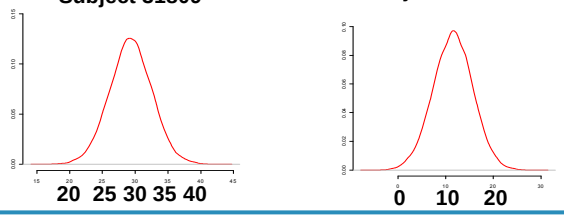
Posterior mean for each missing Y_{12}

Observed + imputed

subjid	trtcd	trtn	y1	y12
30111	F	7	15	14.000000
30501	F	7	16	13.000000
30509	F	7	26	17.000000
30516	F	7	28	19.000000
30601	F	7	36	31.000000
30613	F	7	18	11.512219
30901	F	7	13	5.000000
31107	F	7	30	29.000000
31204	F	7	13	15.000000
31206	F	7	20	21.000000
31208	F	7	16	11.000000
31603	F	7	19	12.000000
31701	F	7	21	4.000000
31705	F	7	6	11.000000
31809	F	7	27	29.318484
⋮				

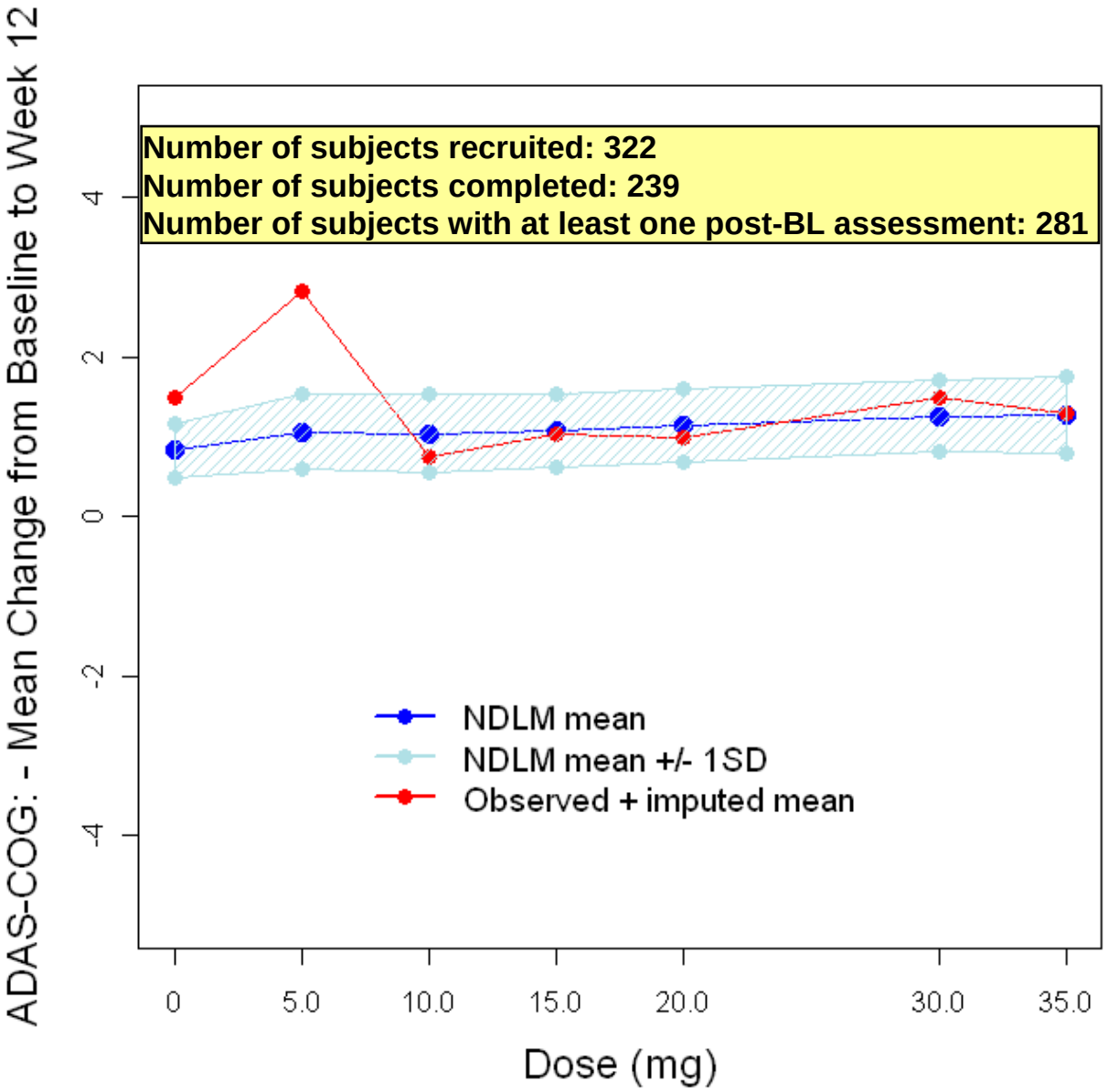
R2WinBUGS

Longitudinal Models and Bayesian Imputation

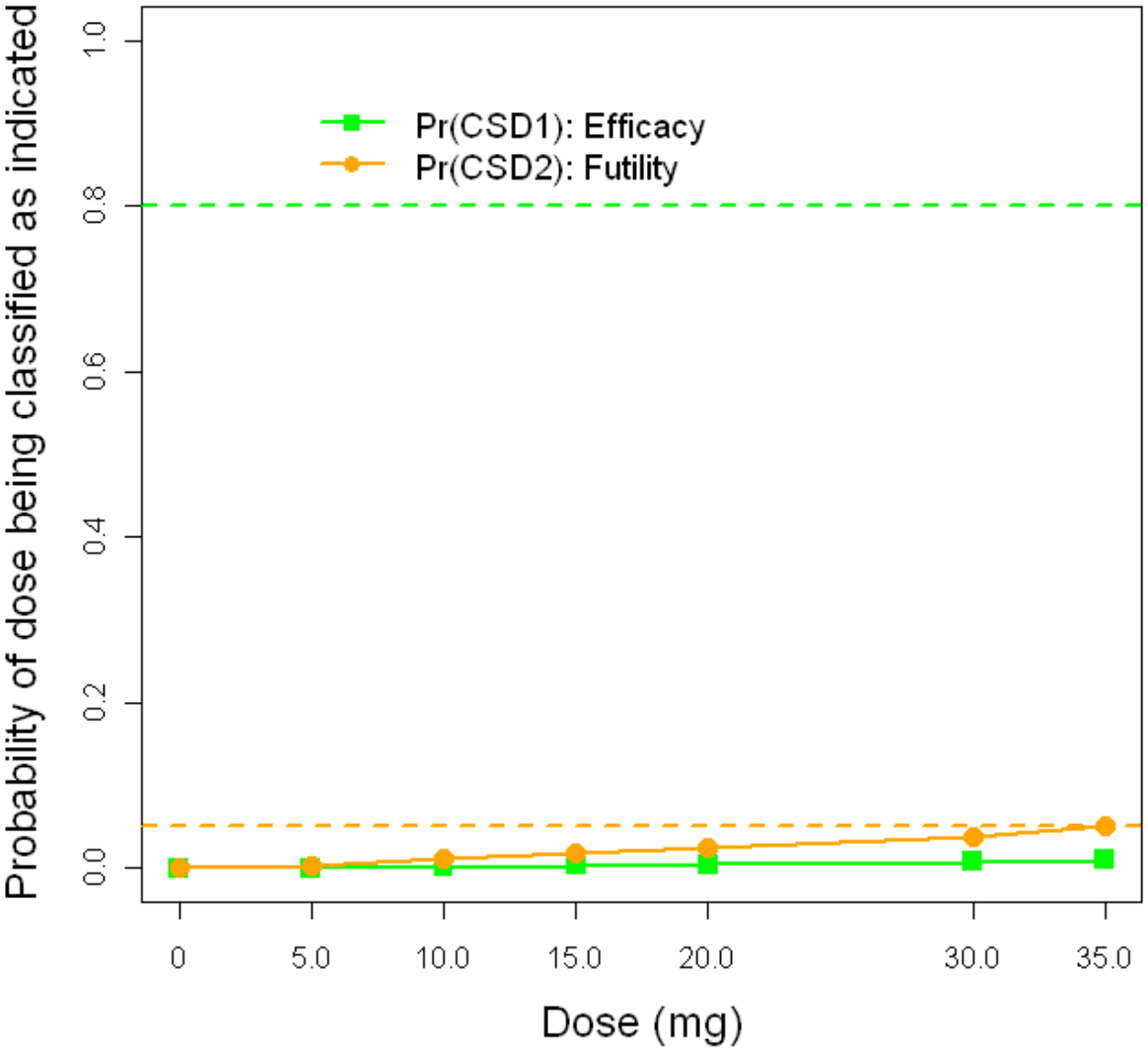


Posterior distribution of missing Y_{12}

DR Curve – Longitudinal Model and NDLM: N=281



Probability of Success
Longitudinal Model and NDLM: N=281



Summary

- Bayesian approach facilitates decision-making in early drug development using totality of data at an interim stage in a clinical trial.
- Evaluation of probability of success require complex computations, which can be easily handled these days using R and WinBUGS through R2WinBUGS.
- Dose-response model exploits relationship among adjacent doses and longitudinal model exploits relationship among observed responses at different time point for a dose.
- Our algorithm can also be applied for fitting other dose-response models.