Drug demand forecasting R shiny app manual

1 Introduction

The R Shiny application provides a reliable and flexible tool for predicting enrollment, treatment discontinuation, and drug demand in clinical trials. The application can be utilized at different stages of a clinical trial, including the design stage, real-time before enrollment completion, and real-time after enrollment completion.

The app's versatility is due to its ability to accommodate various enrollment, event, and drug dispensing models. These models' assumptions are clearly outlined to ensure the app's predictions are accurate and reliable.

Users must provide relevant study data as input to the application, and it provides predictions as output.

2 Enrollment models

In this study, we adopt a Poisson enrollment process to model the number of subjects enrolled in a clinical trial over different time periods. This process assumes that the number of subjects enrolled during each period is statistically independent.

We use the function $a(t)$ to represent the enrollment rate on day t since the start of the trial. The number of subjects enrolled between day t_0 and day t_1 follows a Poisson distribution with mean

$$\mu(t_1) - \mu(t_0) = \int_{t_0}^{t_1} a(u)\, du$$

where $\mu(t)$ is the integral of $a(u)$ from 0 to t.

Different enrollment models assume different functional forms for $a(t)$ and $\mu(t)$. By selecting an appropriate enrollment model, we can estimate the enrollment rate and predict the number of subjects likely to be enrolled at different stages of the trial.

2.1 The Poisson enrollment model

The homogeneous Poisson enrollment model assumes a constant enrollment rate, i.e., $a(t) \equiv \mu$. The mean number of subjects enrolled by time t is given by $\mu(t) = \mu t$.

2.2 The time-decay enrollment model

The time-decay enrollment model assumes that $a(t) = \frac{\mu}{\delta}\left(1 - e^{-\delta t}\right)$, where μ is the base rate parameter and δ is the decay rate parameter. The enrollment rate begins at $a(0) = 0$ and increases to a steady state value of $a(\infty) = \mu/\delta$ as t approaches infinity. The mean number of subjects enrolled by time t is given by $\mu(t) = \frac{\mu}{\delta}\left(t - \frac{1}{\delta}\left(1 - e^{-\delta t}\right)\right)$.

2.3 The B-spline enrollment model

The B-spline enrollment model is proposed to address the limitations of the time-decay enrollment model, particularly in capturing complex enrollment patterns where the rate of enrollment initially increases and then decreases. The B-spline function is employed to model the log enrollment rates to maintain the positivity of the enrollment rate. The B-spline model requires users to specify the number of inner knots and the number of days used for averaging enrollment rates before the last enrollment date (lag days) to make predictions. The application of log transformation and lag days are introduced to enhance the B-spline enrollment model proposed by Zhang and Long (2010).

The B-spline enrollment model can only be used after the trial has started and the enrollment is ongoing. It cannot be used at the design stage.

2.4 The piecewise Poisson enrollment model

The piecewise Poisson model is a widely used enrollment model that segments the time axis into multiple intervals, each characterized by a constant enrollment rate. Despite its lack of smoothness, the piecewise Poisson model is a flexible and powerful tool for specifying and analyzing enrollment trends in clinical trials.

2.5 Generation of enrollment times

Suppose that the study is in progress at time t_0, and $n(t_0)$ subjects have already been enrolled, with a target enrollment of n subjects. Therefore, the number of new subjects to enroll is $r = n - n(t_0)$. The Poisson enrollment process assumes statistical independence of the number of enrollments in separate time intervals. Let $n(t)$ represent the total number of enrolled subjects by time t, and $V_{(i)}$ denote the enrollment time for the ith new subjects. It is evident that

$$P\big(V_{(i)} > v_1 \big| V_{(i-1)} = v_0\big) = P(n(v_1) - n(v_0) = 0) = \exp\big(-\mu(v_1) + \mu(v_0)\big)$$

Using the inverse transform method, we can generate the enrollment times for the r new subjects sequentially as follows:

- Generate e_1 from a standard exponential distribution, and calculate $V_{(1)} = \mu^{-1}(\mu(t_0) + e_1)$.
- For $i = 2, \ldots, r$, generate e_i from a standard exponential distribution, and set $V_{(i)} = \mu^{-1}(\mu\big(V_{(i-1)} + e_i\big)$.

3 Event models

In the context of treatment prediction, the event is treatment discontinuation. Let W denote the time between enrollment and event for a subject. We can characterize the random variable W using either the survival function, $S(t) = P(W > t)$, or the hazard rate function,

$$h(t) = \lim_{\Delta t \to 0} \frac{P(T \le t + \Delta t | T > t)}{\Delta t}$$

The hazard rate function tells us the instantaneous rate of having the event at any given time, given that the subject has not discontinued treatment before that time.

3.1 The exponential distribution

The exponential distribution is the most basic time-to-event distribution that assumes a constant hazard rate over time, which can be denoted as $h(t) \equiv \lambda$. The corresponding survival function is $S(t) = e^{-\lambda t}$. For instance, if we have an event rate of 5% in one year, this can be translated to an exponential event distribution with a hazard rate of $\lambda = -\frac{\log(S(t))}{t} = -\frac{\log(1-0.05)}{365} = 0.00014$ per day. The median of the exponential distribution is $\frac{\log(2)}{\lambda}$.

3.2 The Weibull distribution

The Weibull distribution is a more versatile version of the exponential distribution. Unlike the exponential distribution, it does not assume a constant hazard rate, making it more widely applicable. This distribution is defined by two parameters, κ and λ, where κ determines the shape of the distribution curve and λ determines its scaling. These parameters are referred to as the shape and scale parameters, respectively.

The hazard function of the Weibull distribution can be expressed as

$$h(t) = \frac{\kappa}{\lambda}\left(\frac{t}{\lambda}\right)^{\kappa-1}$$

When $\kappa = 1$, the hazard rate remains constant over time, which is the same as the exponential case. However, when $\kappa > 1$, the hazard rate increases as time goes on, whereas it decreases when $\kappa < 1$.

The survivor function for the Weibull distribution is

$$S(t) = e^{-\left(\frac{t}{\lambda}\right)^{\kappa}}$$

The mean of the Weibull distribution is $\lambda\Gamma\left(1+\frac{1}{\kappa}\right)$ and the variance is $\lambda^2\left(\Gamma\left(1+\frac{2}{\kappa}\right) - \Gamma^2\left(1+\frac{1}{\kappa}\right)\right)$, where $\Gamma(\cdot)$ is the gamma function.

3.3 The log-logistic distribution

The log-logistic distribution is a probability distribution that models a variable whose logarithm follows a logistic distribution, i.e., $T \sim llogis(\mu, \sigma^2)$ if $\log(T) \sim logis(\mu, \sigma^2)$. Unlike the Weibull distribution, which has a monotonically increasing or decreasing hazard rate, the hazard rate function of the log-logistic distribution initially increases from zero to a maximum and then decreases to zero as time approaches infinity. The log-logistic distribution generally has heavier tails than the Weibull distribution. This means that there is a relatively higher probability of observing extreme values for a log-logistic random variable than for a Weibull random variable. The survival function of the log-logistic distribution is

$$S(t) = \frac{1}{1+\exp\left(\frac{\log(t)-\mu}{\sigma}\right)} = \frac{1}{1+\left(\frac{t}{\lambda}\right)^{\kappa}}$$

where $\kappa = \frac{1}{\sigma}$ is the shape parameter of the log-logistic distribution, and $\lambda = \exp(\mu)$ is the scale parameter of the log-logistic distribution.

The mean of the log-logistic distribution exists if $\kappa > 1$ and the variance of the log-logistic distribution exists if $\kappa > 2$.

3.4 The log-normal distribution

The log-normal distribution is a probability distribution that models a variable whose logarithm follows a normal distribution, i.e., $T \sim lnorm(\mu, \sigma^2)$ if $\log(T) \sim N(\mu, \sigma^2)$. Unlike the Weibull distribution, which has a monotonically increasing or decreasing hazard rate, the hazard rate function of the log-normal distribution initially increases from zero to a maximum and then decreases to zero as time approaches infinity. The log-normal distribution generally has heavier tails than the Weibull distribution. This means that there is a relatively higher probability of observing extreme values for a log-normal random variable than for a Weibull random variable. The survival function of the log-normal distribution is

$$S(t) = 1 - \Phi\left(\frac{\log(t) - \mu}{\sigma}\right)$$

where $\Phi(\cdot)$ is the distribution function of the standard normal distribution.

The mean of the log-normal distribution is $\exp\left(\mu + \frac{1}{2}\sigma^2\right)$ and the variance of the log-normal distribution is $(\exp(\sigma^2) - 1)\exp(2\mu + \sigma^2)$.

3.5 The piecewise exponential distribution

The piecewise exponential distribution divides the time axis into multiple intervals, each characterized by a constant hazard rate. This allows the hazard rate to change over time and hence is more flexible than the exponential distribution.

3.6 The model-averaging event distribution

To perform model-averaging, we model the time-to-event using two distributions: Weibull and log-normal. The weights for each distribution are determined based on the Bayesian Information Criterion (BIC) score. This approach seeks to balance and improve the robustness of the model by combining the strengths of both parametric models. The survival function of the resulting averaged model takes the following form

$$S(t) = w_{WB}S_{WB}(t) + w_{LN}S_{LN}(t)$$

where w_{WB} and w_{LN} are the weights for the Weibull and log-normal distributions, respectively,

$$w_{WB} = \frac{\exp\left(-\frac{1}{2}BIC_{WB}\right)}{\exp\left(-\frac{1}{2}BIC_{WB}\right) + \exp\left(-\frac{1}{2}BIC_{LN}\right)}$$

$w_{LN} = 1 - w_{WB}$, and BIC_{WB} and BIC_{LN} are the BIC scores for the respective models.

BIC is a statistical measure used for model selection among a set of candidate models. It is a criterion for model selection that balances model fit against model complexity. Among competing models, the one that achieves the lowest BIC value is typically preferred as it indicates a better balance between model complexity and goodness of fit.

We utilize a weighted BIC to evaluate the performance of the averaged model. Specifically, we calculate the weighted BIC as $w_{WB}BIC_{WB} + w_{LN}BIC_{LN}$.

3.7 The spline event model

In the spline event model developed by Royston and Parmar (2002), a transformed survival function, $g\big(S(t)\big)$, is modelled as a natural cubic spline function of log time $x = \log(t)$,

$$g\big(S(t)\big) = s(x, \gamma)$$

In the proportional hazards model (`scale = "hazard"`), $g\big(S(t)\big) = \log\big(-log\big(S(t)\big)\big)$.

In the proportional odds model (`scale = "odds"`), $g\big(S(t)\big) = \log\left(\frac{1}{S(t)} - 1\right)$.

In the probit model (`scale = "normal"`), $g\big(S(t)\big) = -\Phi^{-1}\big(S(t)\big)$.

The natural cubic spline is constrained to be linear beyond boundary knots, k_{min} and k_{max}, and is defined as

$$s(x, \gamma) = \gamma_0 + \gamma_1 x + \gamma_2 v_1(x) + \cdots + \gamma_{m+1} v_m(x)$$

where $v_j(x)$ represents the jth basis function:

$$v_j(x) = \big(x - k_j\big)_+^3 - \lambda_j (x - k_{min})_+^3 - \big(1 - \lambda_j\big)(x - k_{max})_+^3$$

Here, k_j is the jth inner knot, $\lambda_j = \frac{k_{max} - k_j}{k_{max} - k_{min}}$, for $j = 1, \ldots, m$. The knots are chosen as equally spaced quantiles of the log uncensored survival times. The boundary knots are chosen as the minimum and maximum log uncensored survival times. In addition, x_+ denotes the positive part of x.

With no knots ($m = 0$), the spline reduces to a linear function, and these models are equivalent to Weibull, log-logistic and log-normal models, respectively. As noted in Royston and Parmar (2002), experience suggests that a worthwhile improvement in fit over a straight-line model is often obtained by using a spline model with a single internal knot, but often little is gained by adding further knots.

3.8 Generation of event times

Assuming a data cutoff time of t_0 for the study, we can generate the underlying event time, W_i, for an ongoing subject i. We know that the enrollment time $U_i \leq t_0$, and that $W_i > t_0 - U_i$. We use the inverse transform method to generate W_i by setting the conditional probability

$$P(W_i > t | W_i > t_0 - U_i, U_i) = \frac{S(t)}{S(t_0 - U_i)}$$

equal to a uniform random variable p_i, so that

$$W_i = S^{-1}(S(t_0 - U_i)p_i)$$

For instance, for the Weibull distribution with a shape parameter κ and a scale parameter λ, the following equation can be used to generate W_i:

$$W_i = \lambda\left(\left(\frac{t_0 - U_i}{\lambda}\right)^{\kappa} + e_i\right)^{1/\kappa}$$

Here $e_i = -\log(p_i)$ is a random variable generated from a standard exponential distribution.

When dealing with the log-normal distribution, it is more efficient to utilize specialized algorithms designed to generate random variables from truncated normal distributions.

To generate the event time from the model averaging event model, we begin by generating the component indicator Y_i from the following Bernoulli distribution,

$$Y_i \sim b\big(1, P(Y_i = 1 | W_i > t_0 - U_i, U_i)\big)$$

where

$$P(Y_i = 1 | W_i > t_0 - U_i, U_i) = \frac{W_{WB} S_{WB}(t_0 - U_i)}{W_{WB} S_{WB}(t_0 - U_i) + W_{LN} S_{LN}(t_0 - U_i)}$$

If $Y_i = 1$, then we generate W_i from the truncated Weibull distribution. If $Y_i = 0$, then we generate W_i from the truncated normal distribution.

3.9 Cumulative number of events

Bagiella and Heitjan (2001) proposed a method to calculate the cumulative number of events by time t in a clinical trial using the following equation:

$$D(t) = D(t_0) + Q(t_0, t) + R(t_0, t)$$

where $D(t_0)$ represents the number of events that have already occurred by time t_0, $Q(t_0, t)$ represents the predicted number of events between t_0 and t from ongoing subjects, and $R(t_0, t)$ represents the predicted number of events between t_0 and t from new subjects.

4 Dosing models

4.1 Dosing schedule

Suppose that there are l drugs in the study. For each drug, we specify the drug name and dose unit. Typically, we use the number of kits as the dose unit for drug demand forecasting. Each drug within the study is associated with a specific dosing schedule. The schedule includes key parameters such as dosing frequency (expressed in terms of the number of days within a treatment cycle, w), the number of kits required per treatment cycle (d), and the maximum number of treatment cycles allowable (N). In general, the dosing frequency remains consistent for all drugs within the same study. However, the number of kits required per treatment cycle may vary among the different drugs in the study.

The total number of kits of a drug given to a subject depends on the treatment cycle the treatment duration x falls into. Suppose that x falls into the jth treatment cycle, then the number of kits to dispense to the subject is

$$\delta(x) = \min(j, N) \times d, \qquad (j-1)w \le x < jw$$

per protocol-specified dosing schedule for the drug.

To predict the number of kits to dispense for a specific drug between the data cut t_0 and a future time t per protocol-specified dosing schedule, we need to consider different scenarios based on subject enrollment and treatment duration.

For subjects who were still taking the drug at time t_0, we calculate the doses to dispense between t_0 and t as follows. Let $Y_i(t_0)$ be an indicator variable that takes the value 1 if subject i was still taking the drug at t_0 and 0 otherwise. Then, the doses to dispense for ongoing subjects can be calculated as

$$B(t_0, t) = \sum_{i=1}^{n(t_0)} Y_i(t_0)\{\delta(\min(W_i, t - U_i)) - \delta(t_0 - U_i)\}$$

where the first term in the braces represents the total doses to dispense to subject i from enrollment to treatment discontinuation or time t, whichever comes first. The second term represents the doses that should have already been dispensed to the subject by cutoff t_0. Therefore, the difference between these terms represents the number of doses to dispense to the subject between t_0 and t.

For new subjects enrolled after the interim analysis, the doses to dispense between t_0 and t can be calculated as

$$C(t_0, t) = \sum_{i=1}^{r} I(V_i \le t)\delta(\min(W_i, t - V_i))$$

where r is the number of new subjects enrolled after t_0, V_i is the enrollment time for the ith new subject, and $I(\cdot)$ is the indicator function.

The calculations presented above rely on two variables: the enrollment time U_i and the event time W_i for each subject i. These variables are either observed or simulated through the algorithms outlined in Sections 2 and 3.

To obtain the total doses of the drug on all treatment arms that contain the drug, we add up the doses dispensed for the drug on each applicable treatment arm.

Table 1 provides an illustration of treatment-by-drug combinations, highlighting the drugs used for each treatment arm.

Table 1 Treatment by drug combinations.

	Drug 1	**Drug 2**
Treatment 1	1	1
Treatment 2	1	0

4.2 Drug dispensing models

The diagram below depicts the drug dispensing history for a typical patient:

$$\text{Randomization } (0) \xrightarrow{T_0} (V_1, d_1) \xrightarrow{k_1, T_1} (V_2, d_2) \xrightarrow{k_2, T_2} (V_3, d_3) \rightarrow (D) \text{ Treatment discontinuation}$$

$$V_i = T_0 + T_1 + \cdots + T_{i-1}$$

4.2.1 Models for T_0

In general, patients were dispensed drugs on the day of randomization or a few days after randomization. Let T_0 denote the number of days between randomization and the first drug dispensing visit. Due to the discreteness of the observed value for T_0, we propose to model T_0 using interval censored survival time analysis, where the interval associated with T_0 is $[T_0, T_0 + 1)$. See Anderson-Bergman (2017) for regression models for interval censored data in R.

We consider the following distributions for the underlying continuous survival time: exponential, Weibull, log-logistic, and log-normal.

4.2.2 Models for k_i

Patients may miss appointments for drug dispensing. Let k_i denote the number of missed appointments between two consecutive drug dispensing visits V_i and V_{i+1}, which can be calculated as

$$k_i = \max\left(\left\lfloor \frac{T_i - \frac{\Delta}{2}}{\Delta} \right\rfloor, 0\right)$$

where Δ is the target number of days between two drug dispensing visits, and T_i is the observed number of days between two drug dispensing visits.

We propose to model k_i using one of the following count models: Poisson, zero-inflated Poisson (ZIP), or negative binomial.

The probability mass function for the ZIP model can be represented as

$$p(y) = \left\{\pi + (1-\pi)e^{-\lambda}\right\} I(y = 0) + (1-\pi)\frac{e^{-\lambda}\lambda^y}{y!} I(y > 0)$$

where π is the probability of extra zeros, and λ is the Poisson rate. See Zeileis, Kleiber and Jackman (2008) for regression models for count data in R.

The negative binomial distribution with size n and probability p has density

$$p(y) = \frac{\Gamma(n+y)}{\Gamma(n)\Gamma(y+1)} p^n (1-p)^y$$

4.2.3 Models for T_i

We propose a linear regression model for T_i given k_i, either using least squares (LS) assuming a normal distribution,

$$T_i \sim N((k_i + 1)\mu_T, \sigma_T^2)$$

or using least absolute deviations (LAD) assuming a Laplace (double exponential) distribution,

$$T_i \sim Laplace\big((k_i + 1)\mu_T, \sigma_T\big)$$

These models capture the variation on T_i around the mean. See Birkes and Dodge (1993) for alternative methods of regression.

4.2.4 Models for d_i

Let d_i denote the number of kits dispensed at the drug dispensing visit V_i. We propose to fit a linear mixed effects model for d_i:

$$d_i|b \sim N(\mu_d + b, \sigma_e^2)$$

where $b \sim N(0, \sigma_b^2)$ is the subject random effect. See McCulloch and Searle (2001) for generalized, linear, and mixed models.

4.2.5 In the presence of visit skipping between randomization and the first drug dispensing visit

If there is visit skipping between randomization and the first drug dispensing visit, i.e., $T_0 \geq \frac{\Delta}{2}$, we model the number of skipped visits between randomization and the first drug dispensing visit, k_0, using a similar count model as k_i, and fit T_0 using a time-to-event model if $k_0 = 0$ and a linear regression model given k_0 is $k_0 > 0$.

5 Input and output

To predict drug dispensation accurately, the required input and the resulting output vary depending on the stage of the study.

5.1 Design stage drug demand forecasting

The following input must be provided:

- The target enrollment (number of subjects)
- The target events
- The level of prediction interval (95%, 90%, or 80%)
- The number of years after study start (prediction horizon)
- What to show on prediction plot: enrollment, event, and/or ongoing
- Predict by treatment
- Predict dosing
- The number of treatment groups
- Treatment allocation in a randomization block
- The number of simulations to be conducted
- The random seed used to initiate the simulations
- The enrollment model for the study (e.g., Poisson, time-decay, or piecewise Poisson) and the corresponding model parameters. These parameters can be based on previous studies, literature reviews, and estimations from sites
- The event model for the study (e.g., exponential, Weibull, log-logistic, log-normal, or piecewise exponential) and the corresponding parameter values by treatment. These parameter values can also be based on previous studies and literature reviews
- The dosing schedule, which includes the number of drugs, drug names and drug units, treatment-by-drug combinations, days per cycle, dose per cycle, and number of cycles for each drug

The following output will be produced:

- Predicted time from trial start until reaching the target number of subjects and events

- Plots of predicted cumulative number of subjects enrolled and cumulative number of treatment discontinuations over time for the overall study and by treatment arm
- Plot of predicted cumulative number of doses to dispense over time by drug per protocol

5.2 Enrollment stage drug demand forecasting

The following input must be provided:

- The target enrollment (number of subjects)
- The target events
- The subject level enrollment and event data set, which includes the following variables:
    - trialsdt: The trial start date
    - usubjid: The unique subject ID
    - randdt: The randomization date for each subject
    - treatment: The treatment group
    - treatment_description: Description of the treatment group
    - time: The number of days elapsed since randomization
    - event: The event indicator, with a value of 1 indicating the occurrence of an event, and 0 indicating no event
    - dropout: The dropout indicator, where 1 corresponds to a dropout and 0 implies no dropout
    - cutoffdt: The cutoff date

- The level of prediction interval (95%, 90%, or 80%)
- The number of years after data cutoff (prediction horizon)
- What to show on prediction plot: enrollment, event, and/or ongoing
- Predict by treatment
- The number of treatment groups

- Predict dosing
- The subject level drug dispensing data, which includes the following variables:
    - usubjid: The unique subject ID
    - visit: The drug dispensing visit, e.g., "Cycle 1 Day 1"
    - date: The date of the drug dispensing visit
    - drug: The numeric code of the drug
    - drug_name: The name of the drug
    - dose_unit: The dose unit for drug dispensing
    - kit_number: The kit number for drug dispensing
    - dispensed_quantity: The number of kits dispensed at the visit
- What to show on dosing prediction plot: model based, and/or protocol based

- Treatment allocation in a randomization block
- The number of simulations to be conducted
- The random seed used to initiate the simulations

- The enrollment model for the study (e.g., Poisson, time-decay, B-spline, or piecewise Poisson)

- The event model for the study (e.g., exponential, Weibull, log-logistic, log-normal, piecewise exponential, model averaging, or spline)

- The dosing schedule, which includes the number of drugs, drug names and drug units, treatment-by-drug combinations, days per cycle, dose per cycle, and number of cycles for each drug
- The model for the time between randomization and the first drug dispensing visit (exponential, Weibull, log-logistic, or log-normal)
- The model for the number of skipped visits between two consecutive drug dispensing visits (Poisson, zero-inflated Poisson, negative binomial)
- The model for the time between two consecutive drug dispensing visits (linear regression)
- The model for the doses dispensed at drug dispensing visits (linear model, or linear mixed-effects model)

The following output will be produced:

- Summary of observed enrollment and event data in terms of the trial start date, data cutoff date, days since trial start, the current number of subjects, events, and ongoing subjects by treatment and for the overall study
- Plot of the observed cumulative number of subjects enrolled and cumulative number of treatment discontinuations over time by treatment arm
- Plot of the daily enrollment rate for the overall study with loess smoothing
- Kaplan-Meier plot for time to treatment discontinuation by treatment arm

- Summary of observed drug dispensing data in terms of the cumulative dose over time by drug
- Plot of cumulative number of doses dispensed over time by drug
- Plot of the observed days between randomization and the first drug dispensing visit
- Plot of the observed days between consecutive drug dispensing visits
- Plot of the observed doses dispensed at drug dispensing visits

- Plot depicting the enrollment model fit for the overall study
- Plot depicting the event model fit by treatment arm

- Plot depicting the time-to-event model fit for the time between randomization and the first drug dispensing visit
- Plot depicting the count model fit for the number of skipped visits between two consecutive drug dispensing visits.
- Plot depicting the linear regression model fit for the time between two consecutive drug dispensing visits
- Plot depicting the linear mixed-effects model fit for the doses dispensed at drug dispensing visits by drug

- Predicted time from cutoff until reaching the target number of subjects
- Predicted time from cutoff until reaching the target number of events

- Plots of observed and predicted cumulative number of subjects enrolled and cumulative number of treatment discontinuations over time for the overall study and by treatment arm
- Plot of observed and predicted cumulative number of doses to dispense over time by drug

5.3 Follow-up stage drug demand forecasting

The following input must be provided:

- The target events
- The subject level enrollment and event data set, which includes the following variables:
    - trialsdt: The trial start date
    - usubjid: The unique subject ID
    - randdt: The randomization date for each subject
    - treatment: The treatment group
    - treatment_description: Description of the treatment group
    - time: The number of days elapsed since randomization
    - event: The event indicator, with a value of 1 indicating the occurrence of an event, and 0 indicating no event
    - dropout: The dropout indicator, where 1 corresponds to a dropout and 0 implies no dropout
    - cutoffdt: The cutoff date

- The level of prediction interval (95%, 90%, or 80%)
- The number of years after data cutoff (prediction horizon)
- What to show on prediction plot: enrollment, event, and/or ongoing
- Predict by treatment
- The number of treatment groups

- Predict dosing
- The subject level drug dispensing data, which includes the following variables:
    - usubjid: The unique subject ID
    - visit: The drug dispensing visit, e.g., "Cycle 1 Day 1"
    - date: The date of the drug dispensing visit
    - drug: The numeric code of the drug
    - drug_name: The name of the drug
    - dose_unit: The dose unit for drug dispensing
    - kit_number: The kit number for drug dispensing
    - dispensed_quantity: The number of kits dispensed at the visit
- What to show on dosing prediction plot: model based, and/or protocol based

- The number of simulations to be conducted
- The random seed used to initiate the simulations

- The event model for the study (e.g., exponential, Weibull, log-logistic, log-normal, piecewise exponential, model averaging, or spline)

- The dosing schedule, which includes the number of drugs, drug names and drug units, treatment-by-drug combinations, days per cycle, dose per cycle, and number of cycles for each drug
- The model for the time between randomization and the first drug dispensing visit (exponential, Weibull, log-logistic, or log-normal)
- The model for the number of skipped visits between two consecutive drug dispensing visits (Poisson, zero-inflated Poisson, negative binomial)
- The model for the time between two consecutive drug dispensing visits (linear regression)
- The model for the doses dispensed at drug dispensing visits (linear model, or linear mixed-effects model)

The following output will be produced:

- Summary of observed enrollment and event data in terms of the trial start date, data cutoff date, days since trial start, the current number of subjects, events, and ongoing subjects by treatment and for the overall study
- Plot of the observed cumulative number of subjects enrolled and cumulative number of treatment discontinuations over time by treatment arm
- Kaplan-Meier plot for time to treatment discontinuation by treatment arm

- Summary of observed drug dispensing data in terms of the cumulative dose over time by drug
- Plot of cumulative number of doses dispensed over time by drug
- Plot of the observed days between randomization and the first drug dispensing visit
- Plot of the observed days between consecutive drug dispensing visits
- Plot of the observed doses dispensed at drug dispensing visits

- Plot depicting the event model fit by treatment arm

- Plot depicting the time-to-event model fit for the time between randomization and the first drug dispensing visit
- Plot depicting the count model fit for the number of skipped visits between two consecutive drug dispensing visits.
- Plot depicting the linear regression model fit for the time between two consecutive drug dispensing visits
- Plot depicting the linear mixed-effects model fit for the doses dispensed at drug dispensing visits by drug

- Predicted time from cutoff until reaching the target number of events
- Plots of observed and predicted cumulative number of subjects enrolled and cumulative number of treatment discontinuations over time for the overall study and by treatment arm
- Plot of observed and predicted cumulative number of doses to dispense over time by drug

For both treatment discontinuation prediction and drug demand forecasting, both summary data and simulated data are available for download.

Except for the input data set, the user inputs can be saved and reused later.

6 References

Emilia Bagiella and Daniel F. Heitjan. Predicting analysis times in randomized clinical trials. *Stat in Med.* 2001; 20:2055-2063.

Xiaoxi Zhang and Qi Long. Stochastic modeling and prediction for accrual in clinical trials. *Stat in Med.* 2010; 29:649-658.

Patrick Royston and Mahesh K. B. Parmar. Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. *Stat in Med.* 2002; 21:2175-2197.

Clifford Anderson-Bergman. icenReg: Regression Models for Interval Censored Data in R. *J Stat Softw.* 2017, Volume 81, Issue 12.

Achim Zeileis, Christian Kleiber, and Simon Jackman. Regression models for count data in R. *J Stat Softw.* 2008, Volume 27, Issue 8.

David Birkes and Yadolah Dodge. *Alternative Methods of Regression*. John Wiley & Sons: New York, 1993.

Charles E. McCulloch and Shayler R. Searle. *Generalized, Linear, and Mixed Models.* John Wiley & Sons: New York, 2001.