Results for PSI poster - A Simulation study of a controlled imputation approach for analyzing missing data in recurrent events due to early discontinuations

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Introduction

Missing data is one of the most critical statistical issues in regulatory science with the ability to impact drug approvals and there are no statistical analysis approaches that can fully replace data that are missing. The treatment effect in a clinical study is often established using an estimand based on the missing at random (MAR) assumption and approaches such as jump to reference (J2R) are sometimes used to provide a conservative estimate that is not based on the MAR assumption. Here we present the results of simulations that were conducted to study the effects of imputation on the estimated treatment effect, its standard error and the power when using different controlled based approaches for recurrent events with different levels of missing data

Imputation Approach

A controlled imputation approach for recurrent events has been developed using a conditional probability relationship between events before and after discontinuation (based on Keene 2014). This method takes into account the observed number of events for a subject with missing data and makes it possible to impute data based on various assumptions. The method is slightly reformulated to allow for a more intuitive way to explore deviations from the MAR assumption, using an algorithm that does not rely on Bayesian methods

- **Jump to reference (J2R)** Missing counts for a subject in either treatment arm will be imputed according to the mean of the placebo arm, conditioned on the subject's observed number of exacerbations.
- **MAR** Missing counts in the benralizumab arm are imputed assuming the expected event rate on benralizumab. Missing data in the placebo arm are assuming the expected event rate using the placebo arm.
- **Delta J2R** Missing counts for a subject in the active treatment arm will be imputed according to a point (determined by delta) between the means of the placebo and active arms, conditioned on the subject's observed number of exacerbations. Missing counts for a subject in the placebo arm will be imputed according to the mean of the placebo arm, conditioned on the subject's observed number of exacerbations.
- **Delta method** : Missing counts for a subject will be imputed according to the mean of the arm that the subject belongs to, conditioned on the subject's observed number of exacerbations and multiplied by a factor delta; In the simulations we have used placebo delta = 1 and active delta = 1.4 which means that, after discontinuation, imputed outcomes will be 40% than expected for a subject with similar history in the placebo group.

Algorithm

1. Estimate model using the observed data,

2. Impute missing data using predictions from the model and the assumption about post withdrawal behaviour,

3. Analyze the multiply-imputed dataset and

4. combine the results using standard MI methodology.

For comparison we estimate the treatment effect using a negative binomial model with the time to discontinuation as an offset term (Direct Likelihood (DL)), which is valid under MAR. We also estimate a negative binomial model using the complete datasets (no missing data)

Data generation model

First, complete data is generated using a negative binomial model, then dropout times are generated based on a model were the individual dropout rate increases as soon as an event occurs. In the simulations we have used a placebo rate of 0.9, a dispersion parameter of 0.9, a treatment effect of 40% event rate reduction and a sample size of 228 subjects per treatment group

We generate 6 different missing data scenarios with increasing dropout rates and 2000 datasets are generated for each scenario. This results in observed dropout rates that differ between the treatment groups:

Table 1: Dropout rates observed in simulations (percent)

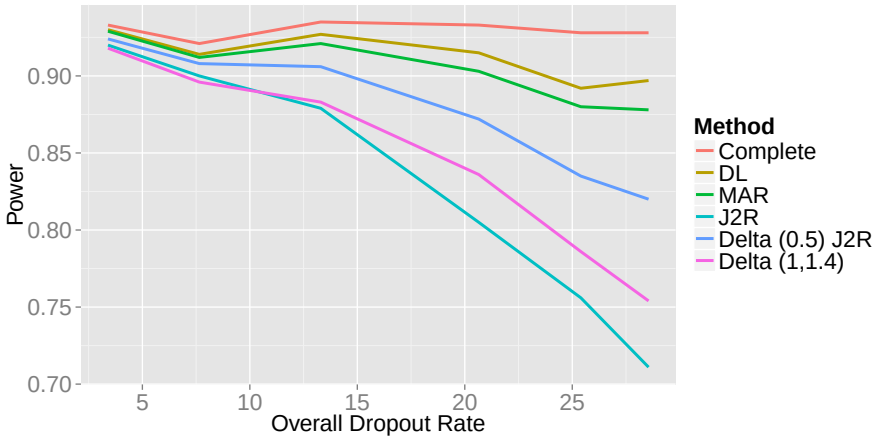
Placebo			Active		
Mean	Q1	Q3	Mean	Q1	Q3
4.2%	3.1%	5.3%	2.6%	1.8%	3.5%
9.4%	7.9%	10.6%	5.9%	4.8%	7%
16.2%	14.5%	18%	10.4%	8.8%	11.8%
24.8%	22.8%	26.8%	16.5%	14.9%	18%
30.2%	28.1%	32.5%	20.6%	18.9%	22.4%
33.8%	31.6%	36%	23.3%	21.5%	25%

Simulation Results

Power

Table 2: Power

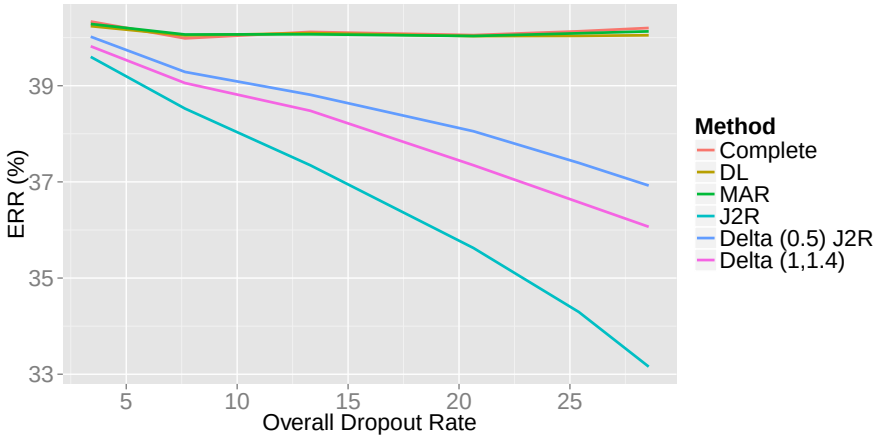
	Complete	DL	J2R	MAR	Delta_J2R	Delta
Scenario 1	0.933	0.930	0.920	0.929	0.924	0.918
Scenario 2	0.921	0.914	0.900	0.912	0.908	0.896
Scenario 3	0.935	0.927	0.879	0.921	0.906	0.883
Scenario 4	0.933	0.915	0.805	0.903	0.872	0.836
Scenario 5	0.928	0.892	0.756	0.880	0.835	0.786
Scenario 6	0.928	0.897	0.711	0.878	0.820	0.754



Event Rate Reduction (ERR)

Table 3: Estimated ERR

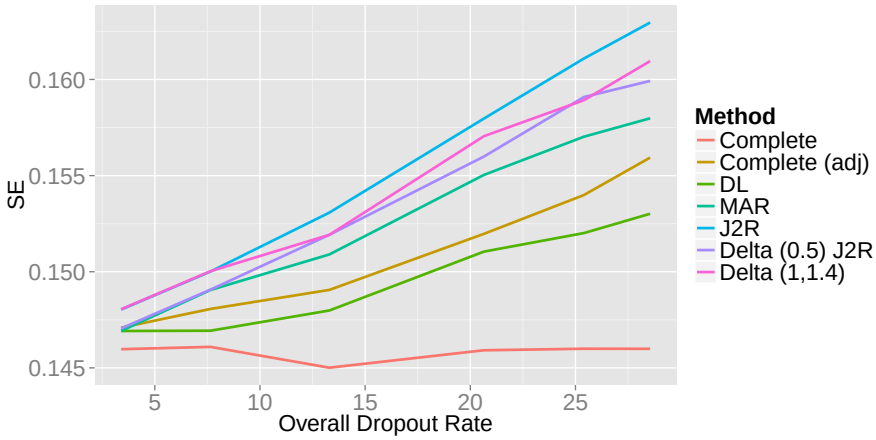
	Complete	DL	J2R	MAR	Delta_J2R	Delta
Scenario 1	40.3	40.3	39.6	40.3	40.0	39.9
Scenario 2	40.0	40.0	38.5	40.0	39.3	39.1
Scenario 3	40.1	40.1	37.4	40.1	38.8	38.4
Scenario 4	40.1	40.1	35.6	40.1	38.0	37.4
Scenario 5	40.1	40.1	34.3	40.1	37.4	36.6
Scenario 6	40.2	40.1	33.2	40.1	36.9	36.0



Standard Error

Table 4: SE

	Complete	DL	J2R	MAR	Delta_J2R	Delta	Compl_adj
Scenario 1	0.146	0.147	0.148	0.147	0.147	0.148	0.147
Scenario 2	0.146	0.147	0.150	0.149	0.149	0.150	0.148
Scenario 3	0.145	0.148	0.153	0.151	0.152	0.152	0.149
Scenario 4	0.146	0.151	0.158	0.155	0.156	0.157	0.152
Scenario 5	0.146	0.152	0.161	0.157	0.159	0.159	0.154
Scenario 6	0.146	0.153	0.163	0.158	0.160	0.161	0.156



[1]

Conclusions

- There is a substantial loss of power when using conservative imputation methods. Firstly because the dilution of the treatment effect that comes from using methods that are conservative, but also because the standard deviation of the treatment effect estimate increases as the imputation method becomes more conservative.
- The estimated AERR for DL and MAR based multiple imputation is very similar to the AERR estimated from complete data and can both be considered unbiased in this case.
- The SE of the estimate using MAR based MI is slightly higher than that of the DL estimate. This is partly due to the low number of imputations used. Both DL and MAR based MI has a higher SE than expected just

[1] The adjusted SE for the complete data is the estimated se divided by the mean follow-up time (maximum=1)

from not observing all events. This is likely due to the data generation model where patients with many events are more likely to drop out.

- Our work offers a view of the consequences of using the J2R and similar approaches when analyzing missing data in recurrent events due to early discontinuations and serves as a reminder that keeping the amount of missing data low is at least as important as how you deal with it; We should design studies to remove or minimise barriers to patients participating so that where it is medically appropriate patients can be maintained on randomised treatment until the outcome data are collected.
- Continuation of missing data research work in various design settings and internal external publications and collaborations are much needed due to the complicated nature of the missing data issue

References

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