

New Multiple Imputation Approaches with SAS

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ABSTRACT

This paper presents a practical implementation of the Jump to Reference (J2R) approach using conditional mean imputation, comparing it to traditional multiple imputation. We describe the methodology, provide SAS® code examples, and summarize results from a simulation study. The goal is to offer a reproducible and computationally efficient alternative for handling missing data in clinical trials, with a focus on accessibility for programmers and statisticians.

INTRODUCTION

Handling missing data is a critical challenge in longitudinal clinical trials. The Jump to Reference (J2R) approach offers a conservative strategy by assuming that patients who discontinue treatment follow the trajectory of the control group from that point onward. This paper explores the implementation of J2R using conditional mean imputation, a deterministic method that avoids random draws while maintaining the statistical properties of multiple imputation.

METHODS

STEP 1: FIT THE IMPUTATION MODEL

We begin by fitting a Mixed Model for Repeated Measures (MMRM) using observed data. The model includes treatment group, visit (categorical), treatment-by-visit interactions, and baseline covariates. The following SAS® code illustrates this step:

```
ods table SolutionF=SF;
proc mixed data=dat;
class TRT01P usubjid avisitn;
model chg=TRT01P TRT01P*avisitn avisitn base / OUTF=outp s;
repeated avisitn/subject=usubjid type=un;
lsmeans TRT01P*avisitn/diff cl;
run;
```

STEP 2: DEFINE THE IMPUTATION STRATEGY

For patients who discontinue treatment, we construct a hybrid trajectory: using expected outcomes under treatment up to discontinuation, and switching to control group expectations thereafter. This reflects the J2R assumption that treatment benefit stops immediately after discontinuation.

```
data SF;
set SF;
where Effect='TRT01P' and TRT01P='Active_treatment';
keep Estimate;
run;

data outpm;
set outp;
if _N_=1 then set SF;
if resid=. and TRT01P= 'Active_treatment' then do;
    chg=Pred-Estimate;
end;
if resid=. and TRT01P^= 'Active_treatment' then do;
    chg=Pred;
end;
run;
```

STEP 3: IMPUTE MISSING VALUES

Conditional mean imputation is not a naive single imputation method. It is mathematically equivalent to maximum likelihood-based multiple imputation with an infinite number of random datasets. This deterministic approach avoids randomness and Monte Carlo error, while preserving the statistical properties of traditional multiple imputation.

STEP 4: ANALYZE THE COMPLETE DATASET

The completed dataset is analyzed using ANCOVA, focusing on the outcome at a specific visit. The model compares treatment and control groups, adjusting for baseline values.

STEP 5: DEFINE THE IMPUTATION STRATEGY

To assess uncertainty, we use resampling methods:

- Jackknife: systematically leave out one subject at a time.
- Bootstrap: randomly resample the data multiple times.

Jackknife is preferred for its speed and stability.

SIMULATION STUDY

We conducted a simulation comparing conditional mean imputation and multiple imputation under the J2R framework. The study evaluated three key metrics:

- Statistical Power
- Type I Error Rate
- 95% Confidence Interval Coverage

Figures from the original slides illustrate the results. Conditional mean imputation showed power and type I error control comparable with the MMRM model run on the dataset with no missing data, with slightly better confidence interval coverage. These results support the use of conditional mean imputation as a reliable and efficient alternative to the multiple imputation.

DISCUSSION

Conditional mean imputation offers a practical and reproducible method for implementing J2R. Unlike multiple imputation, it avoids random draws and seed dependency, making it ideal for programming environments. While both methods preserve type I error and provide reliable estimates, conditional mean imputation is faster and easier to implement in SAS.

CONCLUSION

This paper demonstrates that conditional mean imputation is a robust and efficient method for J2R implementation. It maintains the statistical rigor of multiple imputation while simplifying the programming workflow. We recommend its use in clinical trial settings where reproducibility and computational efficiency are critical.

REFERENCES

Wolbers, Marcel et al. "Standard and reference-based conditional mean imputation." *Pharmaceutical statistics* vol. 21,6 (2022): 1246-1257

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