IMPUTATION OF MISSING DATA IN CLINICAL TRIALS

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WHY DO WE NEED IMPUTATION

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ICH E9: STATISTICAL PRINCIPLES FOR CLINICAL TRIALS

- **Missing values represent a potential source of bias in a clinical trial. Hence, every efforts should be undertaken to fulfill all the requirements of the protocol concerning the collection and management of data.**

- **In reality, however, there will almost always be some missing data ... Unfortunately, no universally applicable methods of handling missing values can be recommended. An investigation should be made concerning the sensitivity of the results of analysis to the method of handling missing values...**

ICH E9: STATISTICAL PRINCIPLES FOR CLINICAL TRIALS

- **Missingness is unavoidable in virtually all clinical trials, no matter how well designed.**
  - Treatment dropout
  - Analysis dropout

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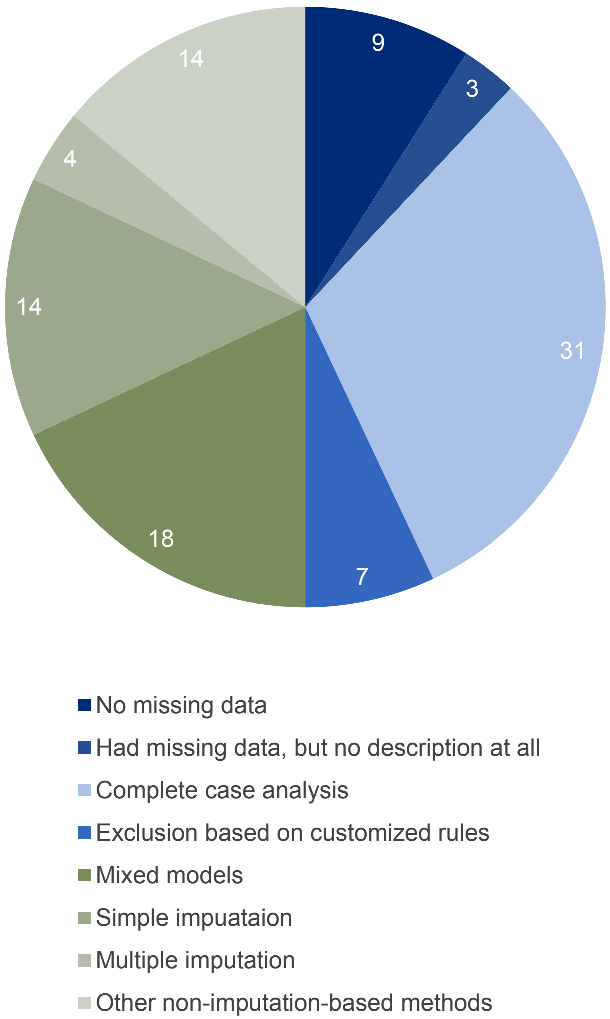
STATUS OF IMPUTATION IN CLINICAL TRIALS

STATUS OF IMPUTATION IN CLINICAL TRIALS



STATUS OF MISSING DATA HANDLING IN 100 ARTICLES FROM TOP JOURNALS

Reference: Powney M, Williamson P, Kirkham J, Kolamunnage-Dona R. A review of the handling of missing longitudinal outcome data in clinical trials. Trials. 2014;15(1):1–19.

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TYPE OF IMPUTATION IN CLINICAL TRIALS

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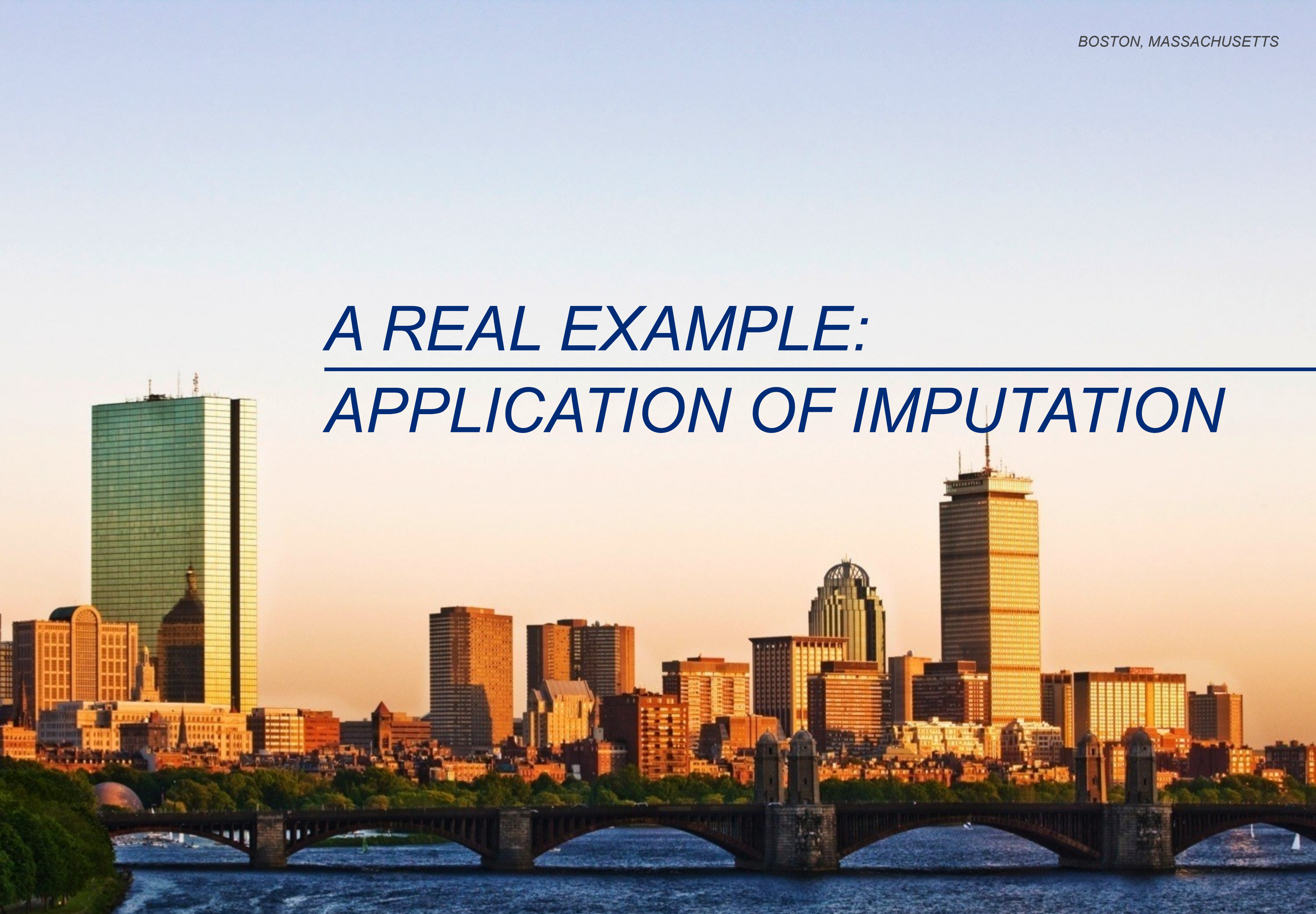
TYPE OF IMPUTATION IN CLINICAL TRIALS

- **Simple/Single Imputation**
- **Multiple Imputation**
  - Proc MI
  - Statistical analysis (Proc MIXED, Proc LOGISTIC etc.)
  - Proc MIANALYZE

BOSTON, MASSACHUSETTS



A REAL EXAMPLE: APPLICATION OF IMPUTATION

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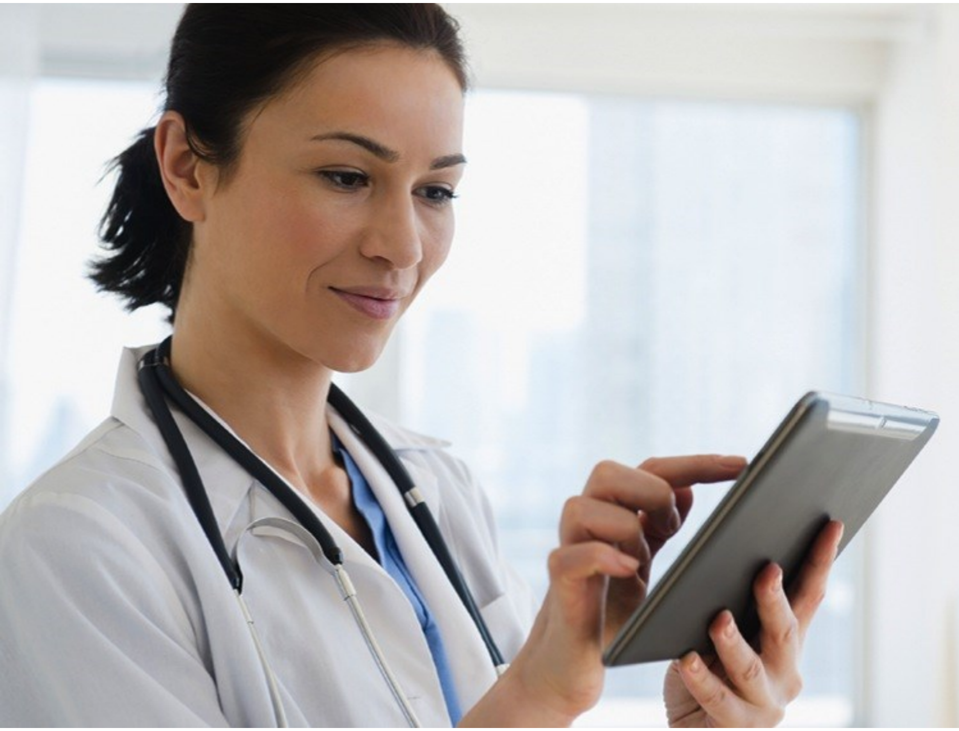
STUDY DESIGN

- Indication: Rheumatoid Arthritis
- Endpoint: ACR20 (American College of Rheumatology 20% response criteria) response rate at week 24
- Design: 60 weeks after Randomization, consisting of 52 weeks of active treatment and 8 weeks of safety follow-up

STUDY DESIGN



- Endpoint:
- Demonstrate equivalence in ACR20 response between Treatment group and Control group at week 24.
  - 95% CI of difference of proportions of subjects achieving ACR20 response is entirely contained within

    [-15%, 15%]

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REAL EXAMPLE: APPLICATION OF IMPUTATION

- **Origin of Missing Data**

Early discontinuation

Definition of Endpoint

1) >=20% improvement from baseline in

TJC & SJC

2) >=20% improvement from baseline at least in 3 of the following 5 criteria

a. SPA score

b. SGA score

c. PGA score

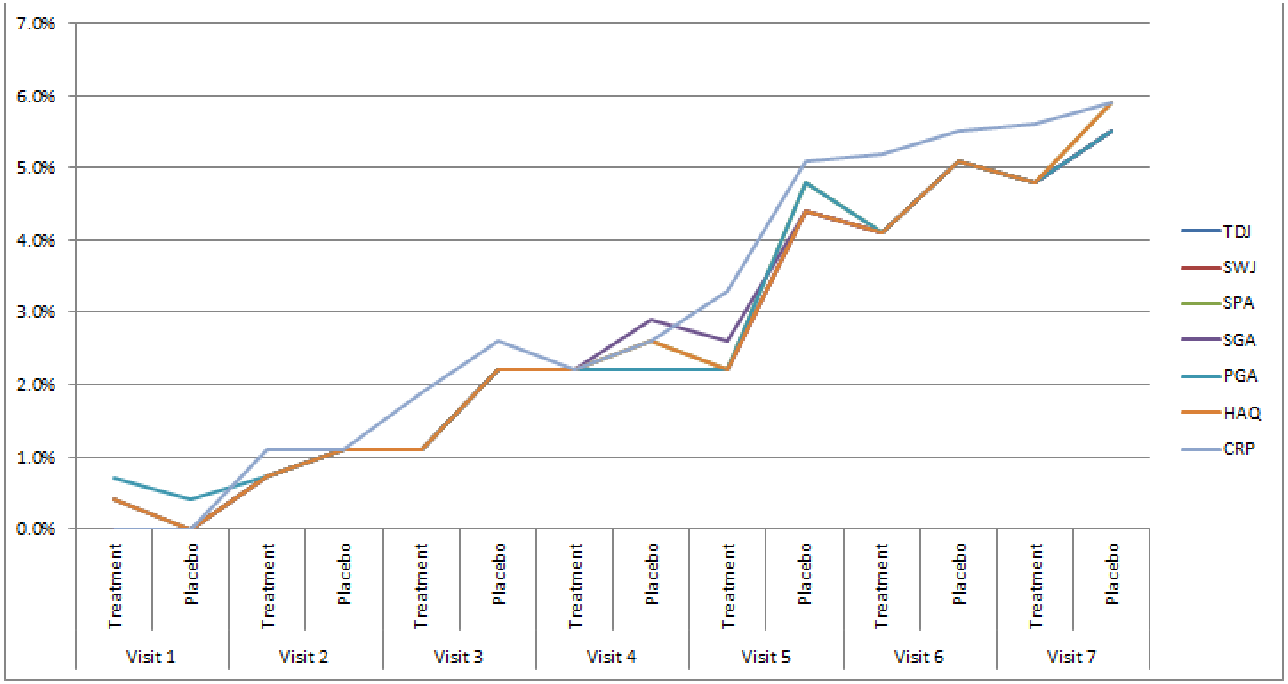
d. HAQ score

e. CRP level

if SJC or TJC is missing, or 3 or more of the above mentioned 5 criteria are missing, ACR20 will be treated as missing.

STATUS OF MISSING DATA

Variable	Treatment	% of Missing
ACR20	Treatment	4.8%
	Placebo	5.5%



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REAL EXAMPLE: APPLICATION OF IMPUTATION

How to impute missing data?

- Multiple imputation (Pattern Mixuture)
  - Missing-at-random (MAR)
  - Missing-not-at-random (MNAR)

REAL EXAMPLE: APPLICATION OF IMPUTATION

How to impute missing data?

MAR

- ✓ Flag the missing values out
- ✓ Impute the non-monotone missing values with partial imputation to get monotone missing pattern
- ✓ Impute missing values with partial imputation to get monotone missing pattern

REAL EXAMPLE: APPLICATION OF IMPUTATION

How to impute missing data?

MNAR

- Delta-adjusted for pattern
  - ✓ If imputation represents improvement, then reduce this improvement by 30%
  - ✓ If imputation represents worsening, then increase this worsen by 30%
  - ✓ If imputation represents zero change, then force categorical or ordinal components to worsening by 1 point (min unit of change)

REAL EXAMPLE: APPLICATION OF IMPUTATION

Sample SAS code & Datasets

Prepare dataset for multiple imputation

- **Proc transpose**, **add flag** for missing data points

One row per subject, per visit, per parameter

↓

One row per subject

REAL EXAMPLE: APPLICATION OF IMPUTATION

Transpose data for MI

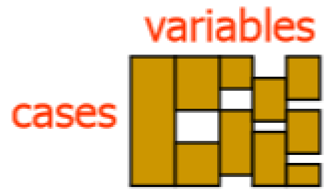
USUBJID	trtn	AVISITN	PARAM	PARAMCD	AVAL
DUMMY004	2	1	Swollen Joint Counts	SWJNT	13
DUMMY004	2	2	Swollen Joint Counts	SWJNT	
DUMMY004	2	3	Swollen Joint Counts	SWJNT	2
DUMMY004	2	4	Swollen Joint Counts	SWJNT	2
DUMMY004	2	5	Swollen Joint Counts	SWJNT	0
DUMMY004	2	6	Swollen Joint Counts	SWJNT	0
DUMMY004	2	7	Swollen Joint Counts	SWJNT	1
DUMMY004	2	8	Swollen Joint Counts	SWJNT	0
DUMMY004	2	9	Swollen Joint Counts	SWJNT	2
DUMMY004	2	10	Swollen Joint Counts	SWJNT	1
DUMMY004	2	1	Tender Joint Counts	TDJNT	23
DUMMY004	2	2	Tender Joint Counts	TDJNT	
DUMMY004	2	3	Tender Joint Counts	TDJNT	5
DUMMY004	2	4	Tender Joint Counts	TDJNT	3
DUMMY004	2	5	Tender Joint Counts	TDJNT	2
DUMMY004	2	6	Tender Joint Counts	TDJNT	1
DUMMY004	2	7	Tender Joint Counts	TDJNT	5
DUMMY004	2	8	Tender Joint Counts	TDJNT	1
DUMMY004	2	9	Tender Joint Counts	TDJNT	3
DUMMY004	2	10	Tender Joint Counts	TDJNT	1

A	B	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X
USUBJID	SITE	trtn	TDJ_1	TDJ_2							TDJ_9	TDJ_10	TDJ_2_fl	TDJ_3_fl						TDJ_9_fl	TDJ_10_fl
DUMMY001	203	1	44										1	1	1	1	1	1	1	1	1
DUMMY002	204	2	21										1	1	1	1	1	1	1	1	1
DUMMY003	401	2	14										1	1	1	1	1	1	1	1	1
DUMMY004	406	2	23		5	3	2	1	5	1	3	1	1								
DUMMY005	407	1	19		#	8	8	0	0	0	0	4	1								

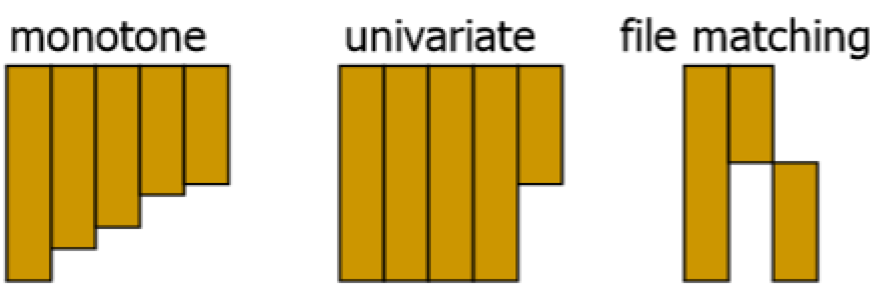
REAL EXAMPLE: APPLICATION OF IMPUTATION

Patterns of Missing Data

General Pattern



Special Patterns



REAL EXAMPLE: APPLICATION OF IMPUTATION

Impute the non-monotone missing values with partial imputation to get monotone missing pattern

```
proc mi data=for_mi1 NIMPUTE=10 seed=12345 out=mi_mono;
       by trtn;
       var site TDJ_1 SWJ_1 SPA_1 SGA_1 PGA_1 HAQ_1 CRP_1
                TDJ_2 SWJ_2 SPA_2 SGA_2 PGA_2 HAQ_2 CRP_2
                TDJ_3 SWJ_3 SPA_3 SGA_3 PGA_3 HAQ_3 CRP_3
                TDJ_4 SWJ_4 SPA_4 SGA_4 PGA_4 HAQ_4 CRP_4
                TDJ_5 SWJ_5 SPA_5 SGA_5 PGA_5 HAQ_5 CRP_5
                TDJ_6 SWJ_6 SPA_6 SGA_6 PGA_6 HAQ_6 CRP_6
                TDJ_7 SWJ_7 SPA_7 SGA_7 PGA_7 HAQ_7 CRP_7
                TDJ_8 SWJ_8 SPA_8 SGA_8 PGA_8 HAQ_8 CRP_8
                TDJ_9 SWJ_9 SPA_9 SGA_9 PGA_9 HAQ_9 CRP_9
                TDJ_10 SWJ_10 SPA_10 SGA_10 PGA_10 HAQ_10 CRP_10;
       mcmc chain=multiple impute=monotone;
run;
```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REAL EXAMPLE: APPLICATION OF IMPUTATION

Impute the non-monotone missing values with partial imputation to get monotone missing pattern

```
proc mi data=for_mi1 NIMPUTE=10 seed=12345 out=mi_mono;
      by trtn;
      var site TDJ_1 SWJ_1 SPA_1 SGA_1 PGA_1 HAQ_1 CRP_1
               TDJ_2 SWJ_2 SPA_2 SGA_2 PGA_2 HAQ_2 CRP_2
               TDJ_3 SWJ_3 SPA_3 SGA_3 PGA_3 HAQ_3 CRP_3
               TDJ_4 SWJ_4 SPA_4 SGA_4 PGA_4 HAQ_4 CRP_4
               TDJ_5 SWJ_5 SPA_5 SGA_5 PGA_5 HAQ_5 CRP_5
               TDJ_6 SWJ_6 SPA_6 SGA_6 PGA_6 HAQ_6 CRP_6
               TDJ_7 SWJ_7 SPA_7 SGA_7 PGA_7 HAQ_7 CRP_7
               TDJ_8 SWJ_8 SPA_8 SGA_8 PGA_8 HAQ_8 CRP_8
               TDJ_9 SWJ_9 SPA_9 SGA_9 PGA_9 HAQ_9 CRP_9
               TDJ_10 SWJ_10 SPA_10 SGA_10 PGA_10 HAQ_10 CRP_10;
      mcmc chain=multiple impute=monotone;
run;
```


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REAL EXAMPLE: APPLICATION OF IMPUTATION

SAS Output

```
                    The MI Procedure

                   Model Information

Data Set                              WORK.FOR_MI1
Method                                Monotone-data MCMC
Multiple Imputation Chain             Multiple Chains
Initial Estimates for MCMC            EM Posterior Mode
Start                                 Starting Value
Prior                                 Jeffreys
Number of Imputations                 100
Number of Burn-in Iterations          200
Seed for random number generator      1479125490
```

Missing Data Patterns

Group	site	TDJ_1	SWJ_1	SPA_1	SGA_1	PGA_1	HAQ_1	CRP_1	TDJ_2	SWJ_2	SPA_2	SGA_2	PGA_2	HAQ_2	CRP_2	TDJ_3
1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
3	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
4	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
5	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
6	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
7	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
8	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
9	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
10	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
11	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
13	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
14	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	O
15	X	X	X	X	X	X	X	X	.	.	.	.	.	.	.	X
16	X	X	X	X	X	X	X	X	O	O	O	O	O	O	O	O

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REAL EXAMPLE: APPLICATION OF IMPUTATION

SAS Output

Imputation	USUBJID	trtn	TDJ_1	TDJ_2	TDJ_3	TDJ_4	TDJ_5	TDJ_6	TDJ_7	TDJ_8	TDJ_9	TDJ_10	S
1	DUMMY001	1	44										
2	DUMMY001	1	44										
3	DUMMY001	1	44										
4	DUMMY001	1	44										
5	DUMMY001	1	44										
6	DUMMY001	1	44										
7	DUMMY001	1	44										
8	DUMMY001	1	44										
9	DUMMY001	1	44										
10	DUMMY001	1	44										
1	DUMMY004	2	23	14.73481	5	3	2	1	5	1	3	1	
2	DUMMY004	2	23	2.866819	5	3	2	1	5	1	3	1	
3	DUMMY004	2	23	18.6345	5	3	2	1	5	1	3	1	
4	DUMMY004	2	23	2.838253	5	3	2	1	5	1	3	1	
5	DUMMY004	2	23	12.47867	5	3	2	1	5	1	3	1	
6	DUMMY004	2	23	10.8453	5	3	2	1	5	1	3	1	
7	DUMMY004	2	23	15.42317	5	3	2	1	5	1	3	1	
8	DUMMY004	2	23	10.20575	5	3	2	1	5	1	3	1	
9	DUMMY004	2	23	14.27317	5	3	2	1	5	1	3	1	
10	DUMMY004	2	23	16.03699	5	3	2	1	5	1	3	1	
1	DUMMY005	1	19	16.32629	21	8	8	0	0	0	0	4	
2	DUMMY005	1	19	19.91787	21	8	8	0	0	0	0	4	
3	DUMMY005	1	19	7.524593	21	8	8	0	0	0	0	4	
4	DUMMY005	1	19	18.38024	21	8	8	0	0	0	0	4	
5	DUMMY005	1	19	13.45022	21	8	8	0	0	0	0	4	
6	DU[illegible]	[illegible]	19	20.00368	21	8	8	0	0	0	0	4	
7	DUMMY005	1	19	13.25051	21	8	8	0	0	0	0	4	
8	DUMMY005	1	19	19.02346	21	8	8	0	0	0	0	4	
9	DUMMY005	1	19	18.34714	21	8	8	0	0	0	0	4	
10	DUMMY005	1	19	9.277317	21	8	8	0	0	0	0	4	

REAL EXAMPLE: APPLICATION OF IMPUTATION

Impute missing values with monotone missing data

```
proc sort data=mi_mono; by _imputation_; run;

proc mi data=mi_mono out=mi_mono_imp1 nimpute=1 seed=23456;
    by _Imputation_;
    var site TRT01PN TDJ_1 SWJ_1 SPA_1 SGA_1 PGA_1 HAQ_1 CRP_1
        TDJ_2 SWJ_2 SPA_2 SGA_2 PGA_2 HAQ_2 CRP_2
        TDJ_3 SWJ_3 SPA_3 SGA_3 PGA_3 HAQ_3 CRP_3
        TDJ_4 SWJ_4 SPA_4 SGA_4 PGA_4 HAQ_4 CRP_4
        TDJ_5 SWJ_5 SPA_5 SGA_5 PGA_5 HAQ_5 CRP_5
        TDJ_6 SWJ_6 SPA_6 SGA_6 PGA_6 HAQ_6 CRP_6
        TDJ_7 SWJ_7 SPA_7 SGA_7 PGA_7 HAQ_7 CRP_7;
    class site TRT01PN;
    monotone regression;
run;
```

REAL EXAMPLE: APPLICATION OF IMPUTATION

SAS Output

```
                          The MI Procedure

                         Model Information

      Data Set                              WORK.MI_MONO
      Method                                Monotone
      Number of Imputations                 1
      Seed for random number generator      23456


                    Monotone Model Specification

Method        Imputed Variables

Regression    TDJ_1 SWJ_1 SPA_1 SGA_1 PGA_1 HAQ_1 CRP_1 TDJ_2 SWJ_2 SPA_2 SGA_2 PGA_2 HAQ_2 CRP_2 TDJ_3 SWJ_3 SPA_3 SGA_3
              PGA_3 HAQ_3 CRP_3 TDJ_4 SWJ_4 SPA_4 SGA_4 PGA_4 HAQ_4 CRP_4 TDJ_5 SWJ_5 SPA_5 SGA_5 PGA_5 HAQ_5 CRP_5 TDJ_6
              SWJ_6 SPA_6 SGA_6 PGA_6 HAQ_6 CRP_6
Regression    TDJ_7 SWJ_7 SPA_7 SGA_7 PGA_7 HAQ_7 CRP_7
```

REAL EXAMPLE: APPLICATION OF IMPUTATION

SAS Output

Missing Data Patterns

Group	site	TRT01PN	TDJ_1	SWJ_1	SPA_1	SGA_1	PGA_1	HAQ_1	CRP_1	TDJ_2	SWJ_2	SPA_2	SGA_2	PGA_2	HAQ_2	CRP_2
1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
3	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
4	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
5	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
6	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
7	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
8	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
9	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
10	X	X	X	X	X	X	X	X	X	.	.	.	.	.	.	.

Group	TDJ_3	SWJ_3	SPA_3	SGA_3	PGA_3	HAQ_3	CRP_3	TDJ_4	SWJ_4	SPA_4	SGA_4	PGA_4	HAQ_4	CRP_4	TDJ_5	SWJ_5
1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
3	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
4	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
5	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
6	X	X	X	X	X	X	X	X	X	X	X	X	X	X	.	.
7	X	X	X	X	X	X	X	X	X	X	X	X	.	.	.	.
8	X	X	X	X	X	X	X	.	.	.	.	.	.	.	.	.
9	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
10	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

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REAL EXAMPLE: APPLICATION OF IMPUTATION

SAS Output

A	C	G	H	I	J	K	L	M	N	O	P	Q
Imputation	USUBJID	trtn	TDJ_1	TDJ_2	TDJ_3	TDJ_4	TDJ_5	TDJ_6	TDJ_7	TDJ_8	TDJ_9	TDJ_10
1	DUMMY001	1	44	40.51473	32.07224	8.879938	15.82855	17.87598	1.165277	7.899545	1.638709	12.24514
1	DUMMY002	1	27	23	19	10	8	3	3	2	0	0
1	DUMMY003	1	25	25	20	19	14	26	27	27	19	19
1	DUMMY004	1	50	50	38	22	22	20	5	3	0	0
1	DUMMY005	1	33	33	31	28	20	14.48008	4.454857	0.579627	-6.56282	1.831907
1	DUMMY006	1	18	17	13	14	11	10	12	12	12	12
1	DUMMY007	1	17	15	15	14	20	18	13	11	13	11
1	DUMMY008	1	18	18	18	18	18	16	15	21	18	23
1	DUMMY009	1	18	26	24	14	0	0	0	11	11	11
1	DUMMY010	1	16	14	12	16	6	8	1	2	2	2
1	DUMMY011	1	16	12	12	14	14	6	1	2	13	9
1	DUMMY012	1	16	14	14	16	6	0	2	2	0	0
1	DUMMY013	1	14	12	10	5.885943	17.64767	5.855315	1.937029	7.268481	6.943483	15.84456
1	DUMMY014	1	24	29	15	19	8	9	7	4	7	3
1	DUMMY015	1	15	12	1	3	5	5	7	5	8	9

REAL EXAMPLE: APPLICATION OF IMPUTATION

Delta adjustment

- ✓ If imputation represents improvement, then reduce this improvement by 30%
- ✓ If imputation represents worsening, then increase this worsen by 30%
- ✓ If imputation represents zero change, then force categorical or ordinal components to worsening by 1 point (min unit of change)

REAL EXAMPLE: APPLICATION OF IMPUTATION

```
/*visit 2*/
data mi_mono_delta3;
      set mi_mono_impl;
      if TDJ_2_fl=1 and upcase(DSREAS) in ("ADVERSE EVENT","LACK OF EFFICACY") then do;
            if TDJ_2<TDJ_1 then TDJ_2=TDJ_2+(TDJ_1-TDJ_2)*0.3;
            else if TDJ_2>TDJ_1 then TDJ_2=TDJ_2+(TDJ_2-TDJ_1)*0.3;
            else if TDJ_2=TDJ_1 then TDJ_2=TDJ_1+1;
      end;
      /*repeat for the other parameters*/
run;
/*visit 3*/
data mi_mono_delta3;
    set mi_mono_delta3;
    if TDJ_3_fl=1 and upcase(DSREAS) in ("ADVERSE EVENT","LACK OF EFFICACY") then do;
            array fln{2} TDJ_2_fl TDJ_1_fl;
            array TDJ{2} TDJ_2 TDJ_1;
            do i=1 to 2;
                if fln{i}=. then do;
                    TDJ_L=TDJ{i};
                    leave;
                end;
            end;
            if TDJ_L^=. then do;
                if TDJ_3<TDJ_L then TDJ_3=TDJ_3+(TDJ_L-TDJ_3)*0.3;
                else if TDJ_3>TDJ_L then TDJ_3=TDJ_3+(TDJ_3-TDJ_L)*0.3;
                else if TDJ_3=TDJ_L then TDJ_3=TDJ_L+1;
            end;
    end;
    drop i;
    /*repeat for the other parameters*/
run;
```


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REAL EXAMPLE: APPLICATION OF IMPUTATION

Apply statistical analysis model to the imputed dataset, get statistical estimates by _imputation_

Col1	beta	sebeta	lower	upper	_imputation_	trtn
ACR20N	0.0263828	0.0472688	-0.066262	0.119028	1	1
ACR20N	0.0267291	0.0472534	-0.065886	0.1193441	2	1
ACR20N	0.0222079	0.0470665	-0.070041	0.1144564	3	1
ACR20N	0.0334982	0.046575	-0.057787	0.1247835	4	1
ACR20N	0.0189486	0.0471262	-0.073417	0.1113141	5	1
ACR20N	0.0299306	0.046907	-0.062005	0.1218666	6	1
ACR20N	0.0333115	0.0468499	-0.058513	0.1251357	7	1
ACR20N	0.0231251	0.0470255	-0.069043	0.1152933	8	1
ACR20N	0.0306787	0.0471991	-0.06183	0.1231873	9	1
ACR20N	0.0220545	0.0470713	-0.070204	0.1143126	10	1
ACR20N	0.0576289	0.0534323	-0.047097	0.1623543	1	2
ACR20N	0.0494734	0.0537649	-0.055904	0.1548507	2	2
ACR20N	0.0419852	0.0536508	-0.063169	0.1471388	3	2
ACR20N	0.050214	0.0531819	-0.054021	0.1544486	4	2
ACR20N	0.0577646	0.0530677	-0.046246	0.1617754	5	2
ACR20N	0.0419852	0.0536508	-0.063169	0.1471388	6	2
ACR20N	0.0354988	0.0539691	-0.070279	0.1412763	7	2
ACR20N	0.0419852	0.0536508	-0.063169	0.1471388	8	2
ACR20N	0.0574683	0.053564	-0.047515	0.1624518	9	2
ACR20N	0.0419852	0.0536508	-0.063169	0.1471388	10	2
ACR20N	0.0193729	0.0375007	-0.054127	0.0928729	1	3
ACR20N	0.0192258	0.0375924	-0.054454	0.0929055	2	3
ACR20N	0.0076069	0.0371157	-0.065139	0.0803523	3	3
ACR20N	0.0226689	0.0369316	-0.049716	0.0950535	4	3
ACR20N	-0.006687	0.0369407	-0.079089	0.0657159	5	3
ACR20N	0.0190604	0.0370762	-0.053608	0.0917285	6	3
ACR20N	0.018321	0.0368367	-0.053878	0.0905197	7	3
ACR20N	0.0190279	0.0373506	-0.054178	0.0922337	8	3
ACR20N	-0.002985	0.0368613	-0.075232	0.0692613	9	3
ACR20N	0.0114021	0.0372385	-0.061584	0.0843882	10	3

REAL EXAMPLE: APPLICATION OF IMPUTATION

Use PROC MIANALYZE to extract statistical inference

```
proc MIANALYZE data=results;
    ods output ParameterEstimates=main_results;
    modeleffects beta;
    stderr sebeta;
run;
```

REAL EXAMPLE: APPLICATION OF IMPUTATION

SAS Output

The MIANALYZE Procedure

Model Information

Data Set	WORK.RESULTS
Number of Imputations	100

Variance Information

Parameter	Variance Between	Variance Within	Variance Total	DF	Relative Increase in Variance	Fraction Missing Information	Relative Efficiency
beta	0.000065909	0.001523	0.001589	56437	0.043714	0.041917	0.999581

Parameter Estimates

Parameter	Estimate	Std Error	95% Confidence Limits		DF	Minimum	Maximum
beta	-0.002200	0.039867	-0.08034	0.075940	56437	-0.029195	0.015559

Parameter Estimates

Parameter	Theta0	t for H0: Parameter=Theta0	Pr > |t|
beta	0	-0.06	0.9560

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REAL EXAMPLE: APPLICATION OF IMPUTATION

Result

Analysis of ACR20 Response Rate at Week 24; No Imputation (Full Analysis Set)

Treatment	n/n'	(%)	Estimated Difference in Proportions	95% CI
IP (N=269)	183/256	(71.5)	0.03%	[−7.73%, 7.79%]
RP (N=273)	184/258	(71.3)		

Analysis of ACR20 Response Rate at Week 24; Non-responder Analysis (Full Analysis Set)

Treatment	n/n'	(%)	Estimated Difference in Proportions	95% CI
IP (N=269)	183/269	(68.0)	0.8%	[−7.03%, 8.56%]
RP (N=273)	184/273	(67.4)		

Analysis of ACR20 Response Rate at Week 24; Pattern Mixture (Full Analysis Set)

Treatment	n/n'	(%)	Estimated Difference in Proportions	95% CI
IP (N=269)	188/269	(69.9)	-0.2%	[−8.03%, 7.59%]
RP (N=273)	194/273	(71.1)		

N = number of subjects in the Full Analysis Set; n = number of responders; n' = number of subjects with an assessment
ACR20 = American College of Rheumatology 20% response criteria; CI = confidence interval
Nonparametric randomisation-based analysis of covariance was used with region as a stratification factor and baseline CRP value as a covariate.
Subjects with missing ACR20 response at Week 24 were considered as non-responders at Week 24.

REAL EXAMPLE: APPLICATION OF IMPUTATION

Conclusion

- ✓ In analysis with no imputation and a pattern mixture analysis, the adjusted treatment differences in ACR20 response rate were contained within the pre-defined equivalence margins of [-15%, 15%].
- ✓ The equivalence of Treatment group and Control group in terms of ACR20 was shown in the FAS and the robustness of the primary efficacy analysis was further supported.

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Q&A

THANK YOU