The new challenge of clinical trials: estimands, missing data handling and estimation of a treatment effect

Student: Valentine Laizet

Supervisor: Damien Chimits

Date: 10th October 2019

CONTENTS

SERVIER

ENSAI
École nationale
de la statistique
et de l'analyse
de l'information

PRESENTATION OF THE INTERNSHIP

Context

Rising concerns about the impact of intercurrent events and missing data handling on treatment effect estimation

ICH-E9 Guideline → harmonize the principles of statistical methodology applied to clinical trials (1998)

ICH-E9 Guideline **Addendum** on **Estimands** and sensitivity analysis → clarify the clinical trial objectives (draft 2017, final version expected in 2019)

Important definitions

Estimand: clarification of the trial objectives by taking into account **intercurrent events**

- population of interest
- variable of interest
- strategy to handle intercurrent events → **HYPOTHETICAL**
- summary measure

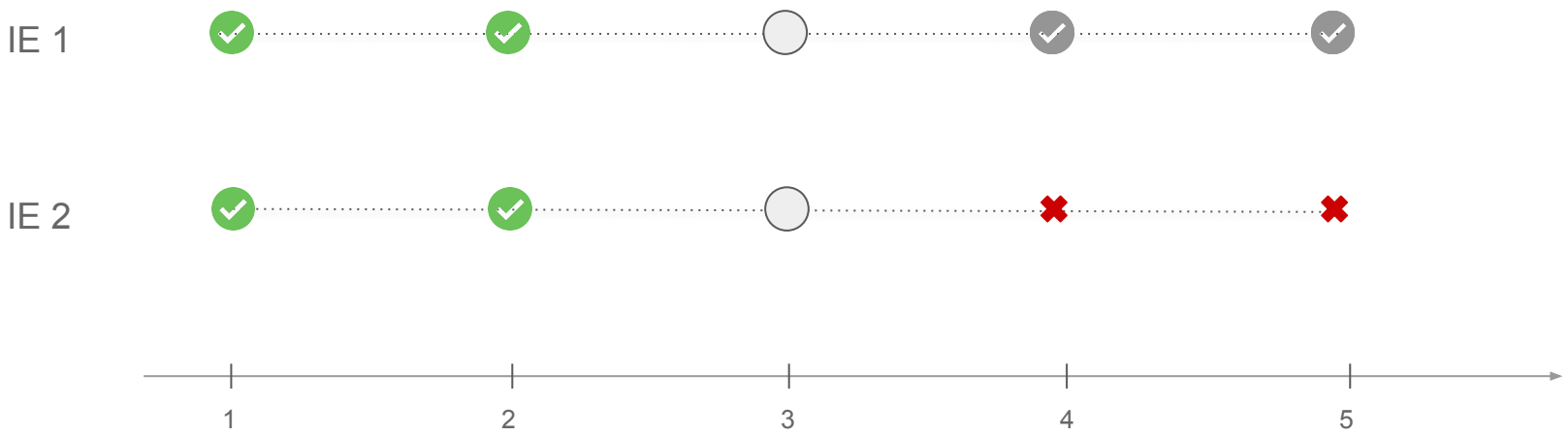
→ *leads to a precise definition of the treatment effect*

Intercurrent events: post-randomization events that may:

- **affect** the interpretation of the variable of interest *(treatment discontinuation due to adverse events...)*
- **prevent** the observation of the variable of interest *(medical procedure...)*

PRESENTATION OF THE INTERNSHIP

Important definitions - *hypothetical strategy*



PRESENTATION OF THE INTERNSHIP

Different steps

1. Intercurrent events handling methods on simulated data set → **two** simulation plans
   - **1)** evaluation of RBI methods: **selection of 2 RBI methods**
   - **2)** analyse of the impact of the **sequencing order of imputation**

2. Literature review on sensitivity analysis for these latter selected methods

3. Application of methods and sensitivity analysis on real data set

Produce recommendations for the use of intercurrent events handling methods

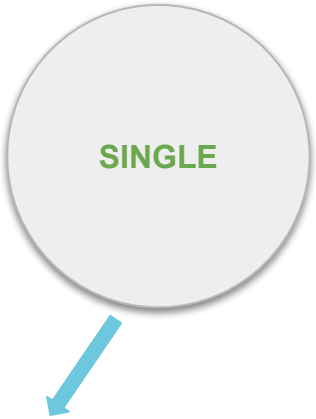
SERVIER

ENSAI
École nationale de la statistique et de l'analyse de l'information

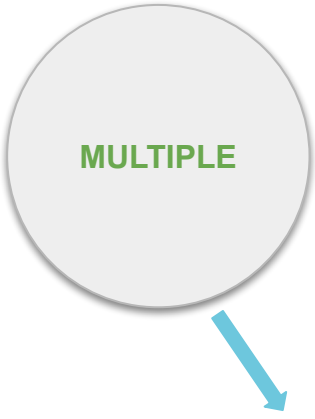
INTERCURRENT EVENTS HANDLING METHODS

Imputation methods

Handling intercurrent events → several hypothetical scenarios → use of **imputation methods**



LOCF (Last Observation Carried Forward),
BOCF (Baseline Information Carried Forward),
LMCF (Last Mean Carried Forward)



distinction regarding the **missingness mechanism**

Multiple imputation methods

- Standard multiple imputation → borrow values from the initially randomized treatment group (**MAR**)
- **Reference-Based imputation** → borrow values from the reference treatment group (placebo) (**MNAR**)

→ Jump to Reference (**J2R**)

→ Copy Increment Reference (**CIR**)

→ Copy Reference (**CR**)

the ***way*** the imputed values are borrowed from the reference group

RBI methods - *theory*

J2R

After deviation

Control profile

CIR

After deviation

Parallel control profile

CR

Before & after deviation

Control profile

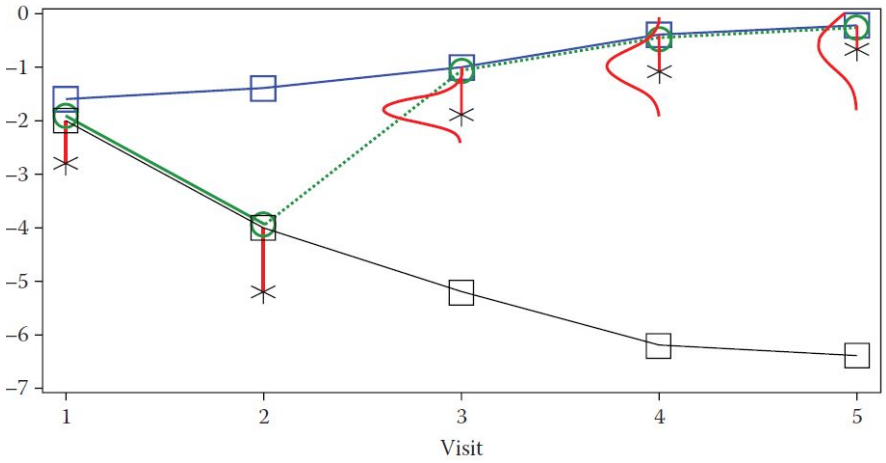
MARGINAL METHODS

starting from the benefit already obtained

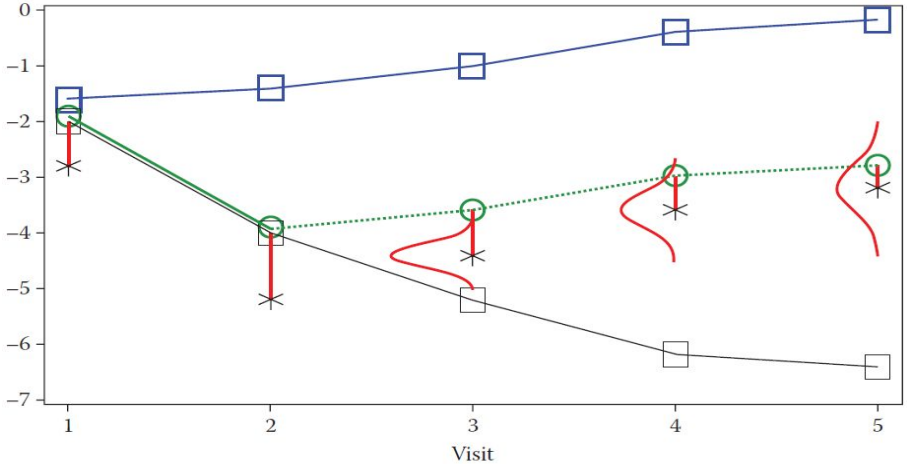
CONDITIONAL METHOD

RBI methods - *illustration* *(Source: Mallinckrodt and Lipkovich. Analyzing longitudinal clinical trial data: A practical guide)*

J2R



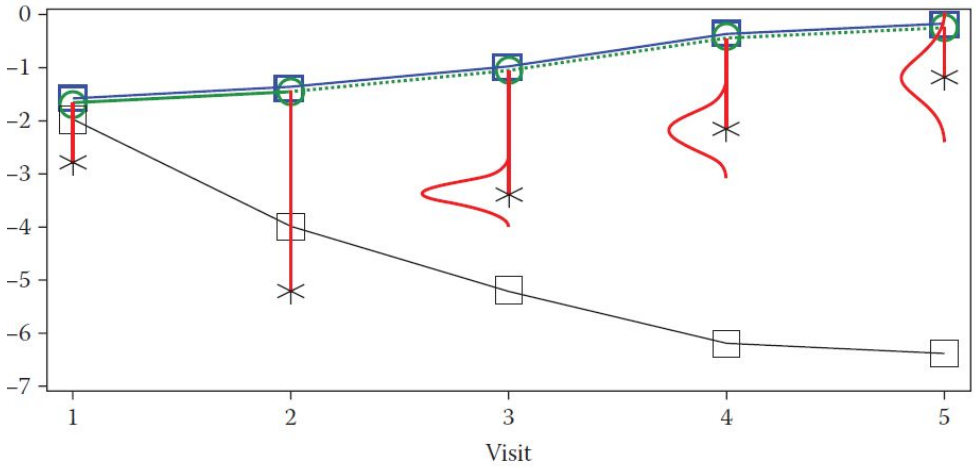
CIR



Drug arm
Placebo arm
Reference arm
Residuals
X Observed/imputed value
Imputation uncertainty

RBI methods - *illustration* *(Source: Mallinckrodt and Lipkovich. Analyzing longitudinal clinical trial data: A practical guide)*

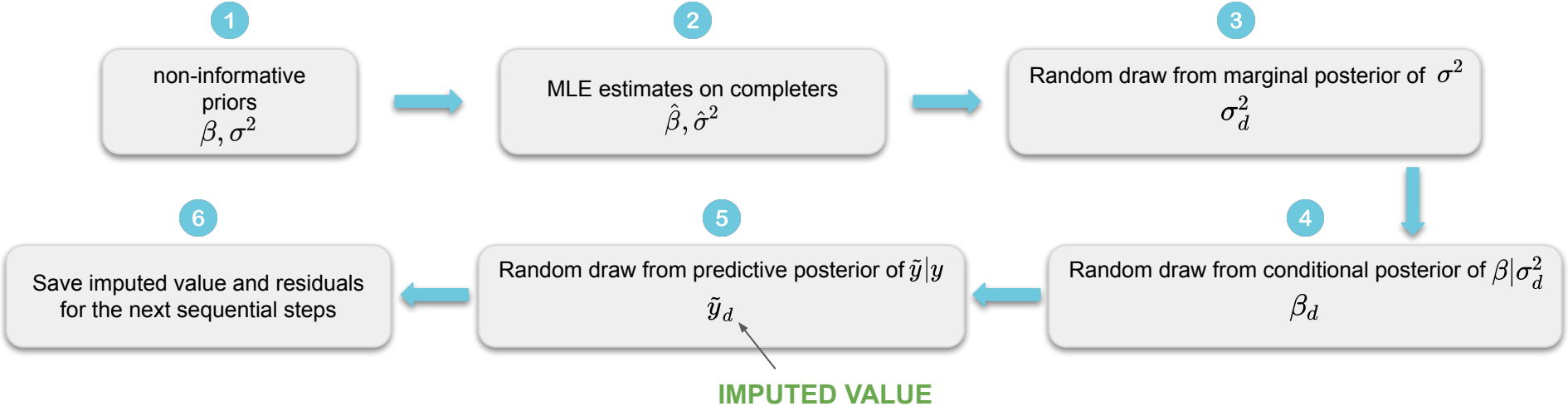
CR



Drug arm
Placebo arm
Reference arm
Residuals
X Observed/imputed value
Imputation uncertainty

METHODS

Multiple imputation sequential algorithm - *Steps to impute one visit measurement*

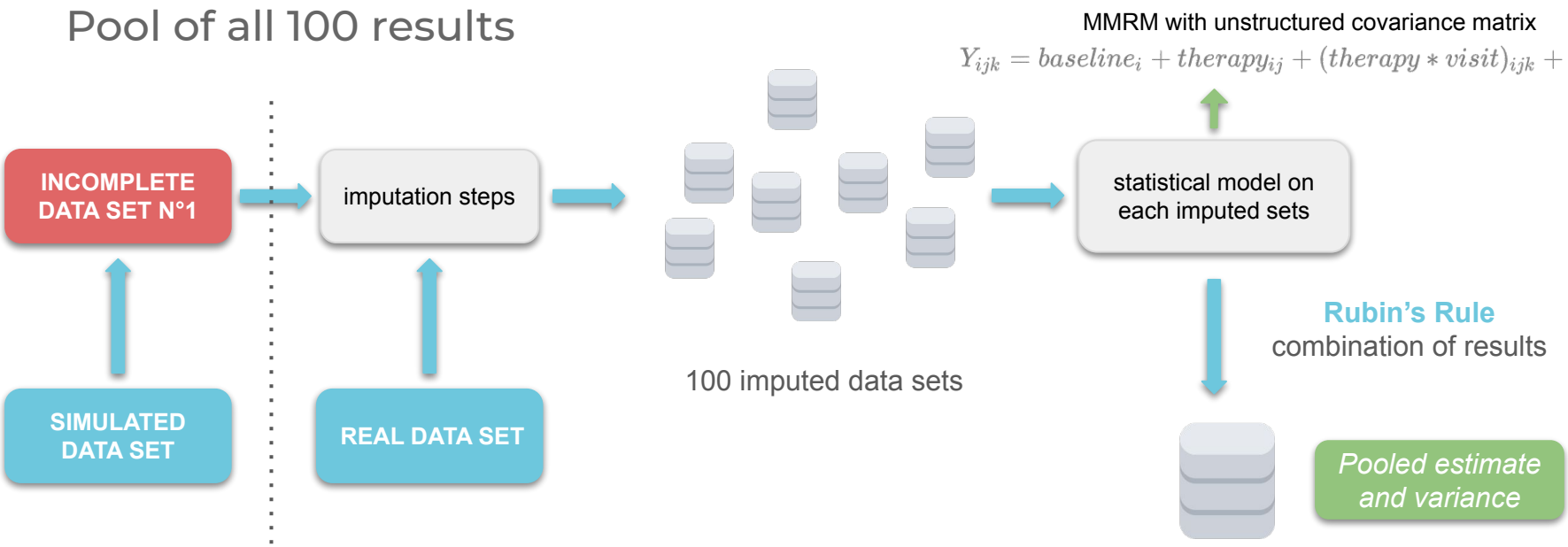


- reiterate **2)** to **5)** for each visit. For example for visit 2, the model for imputed value is:

$$Y_2 = baseline + therapy_2 + imputed_1/residual_1 + \epsilon$$

- reiterate this imputation algorithm to create **100 different imputed datasets**

METHODS

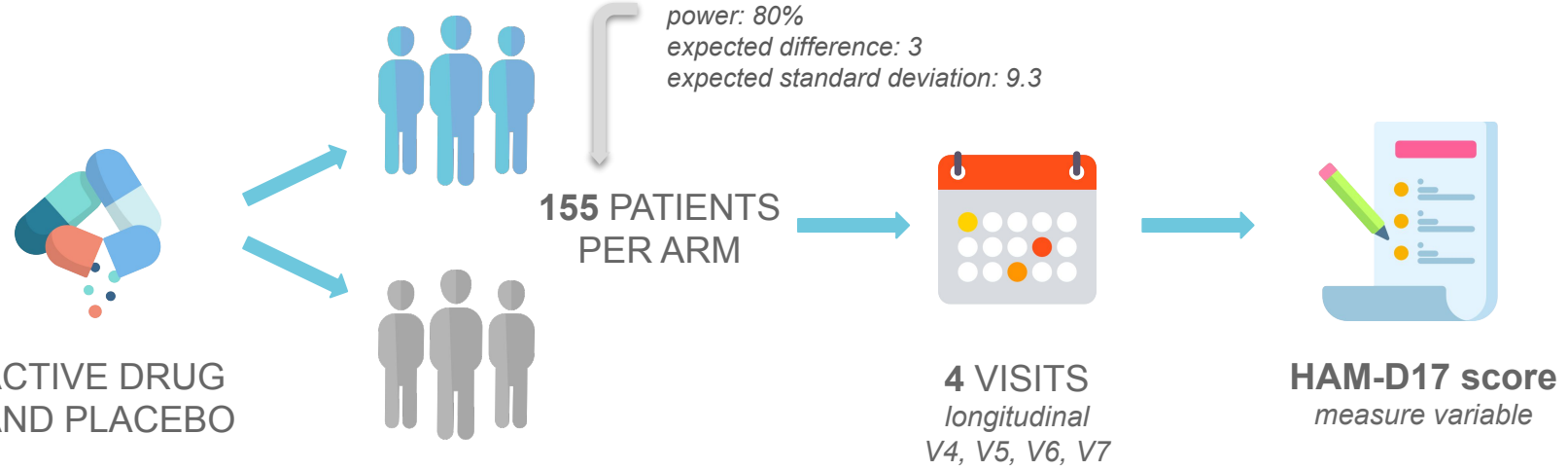


imputation, statistical model application and pool of results for each of the **scenarios** and for the **several simulations**

SIMULATION PLANS & APPLICATION

SIMULATION PLANS & APPLICATION

Simulation of a study in Major Depressive Disorder

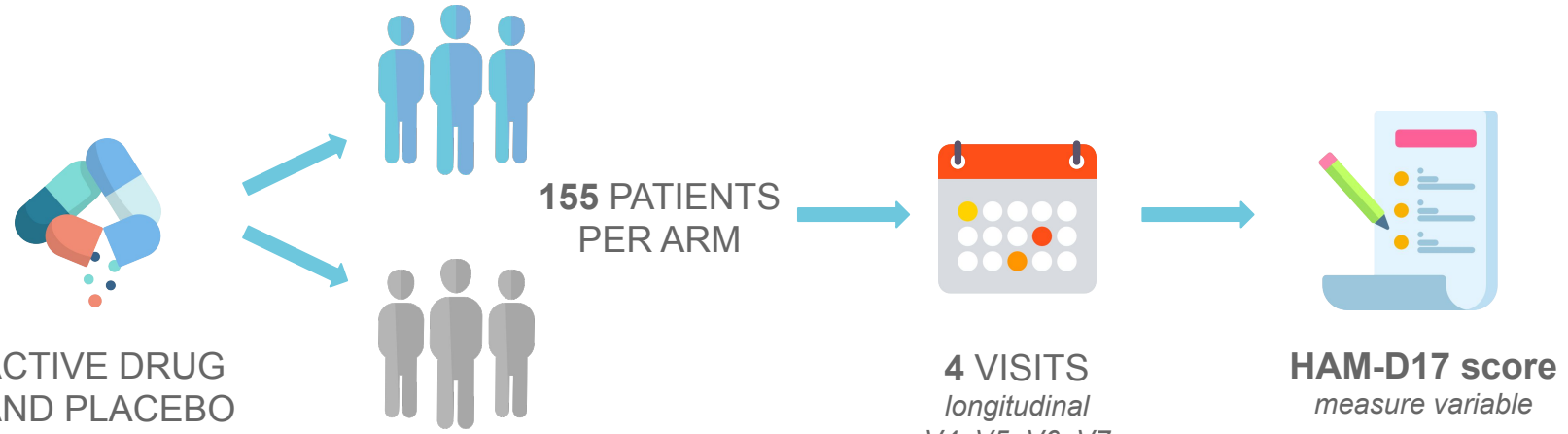


Simulation of a **longitudinal RCT**, based on a real longitudinal antidepressant clinical trial

(James Roger, *London School of Hygiene and Tropical Medecine* - Missing Data - DIA working group, available at: http://missingdata.org.uk/. 2017.)

SIMULATION PLANS & APPLICATION

Simulation of a study in Major Depressive Disorder



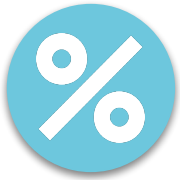
Objective of the fictitious study: assess the efficacy of the active drug compared to placebo in the diminution of the severity level of MDD after 7 weeks of treatment

Primary efficacy variable: change in HAM-D17 score from baseline at final visit (V7)

SIMULATION PLANS & APPLICATION

Two simulation plans

1. Analyse of the impact of **two** variants



missing data
10% to 50%

distribution
between arms

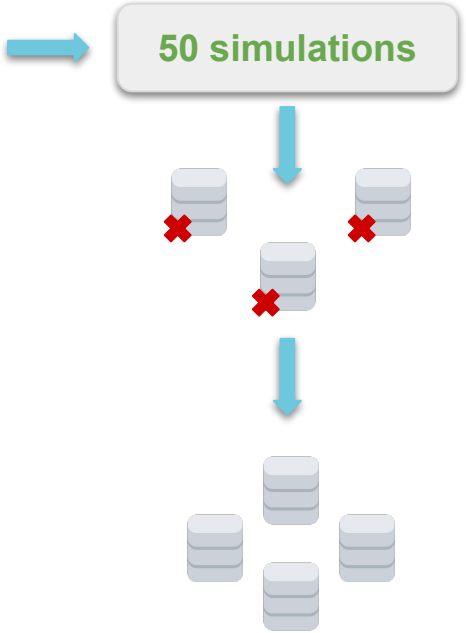
Each combination: one **scenario,** application of **all** methods → Compare results (estimate, variance) → *In fine*: choice of **two** of the three RBI methods for the 2nd simulation plan

Total: 8 scenarios

SIMULATION PLANS & APPLICATION

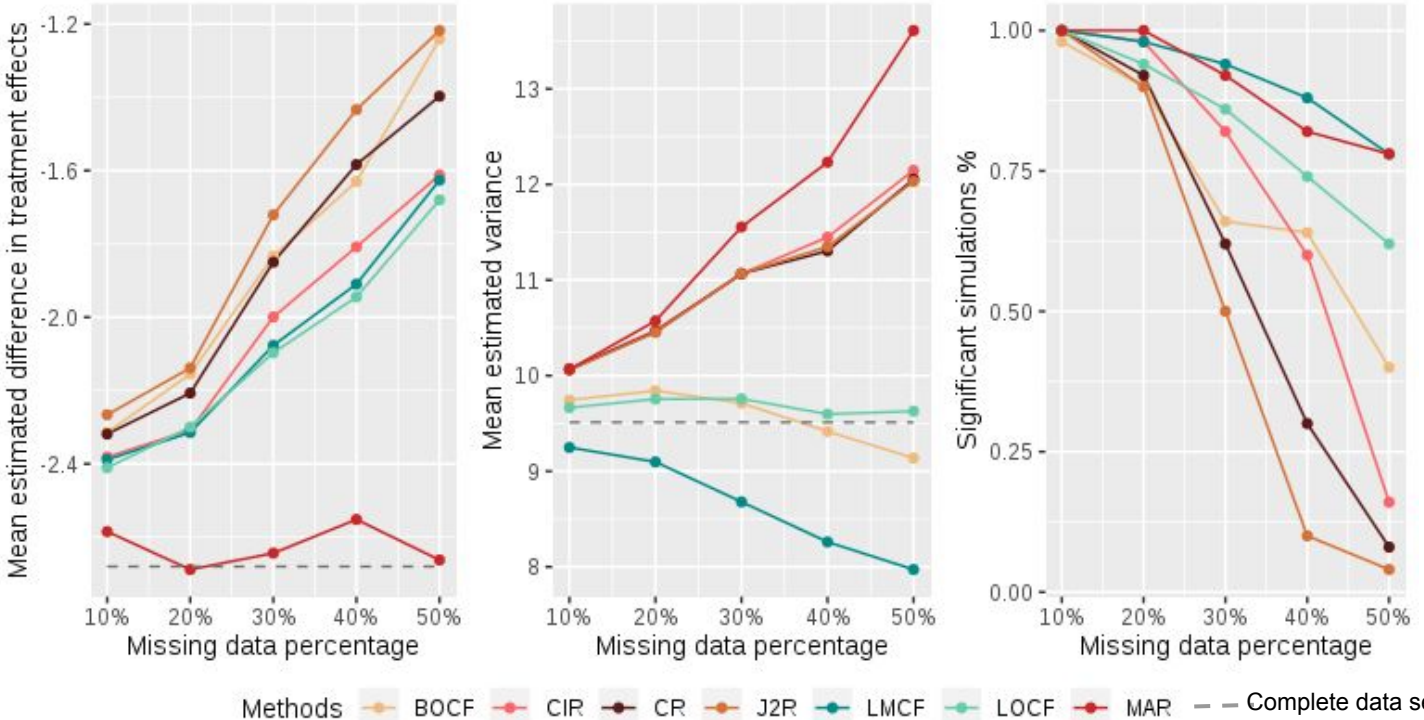
Principal results of the first simulation plan - *presentation of scenarios*

N° scenario	IE distribution			MD%				
	Balanced	Placebo	Drug	10%	20%	30%	40%	50%
00	x			x				
01	x				x			
02	x					x		
03	x						x	
04	x							x
40/02	x					x		
50		x				x		
60			x			x		



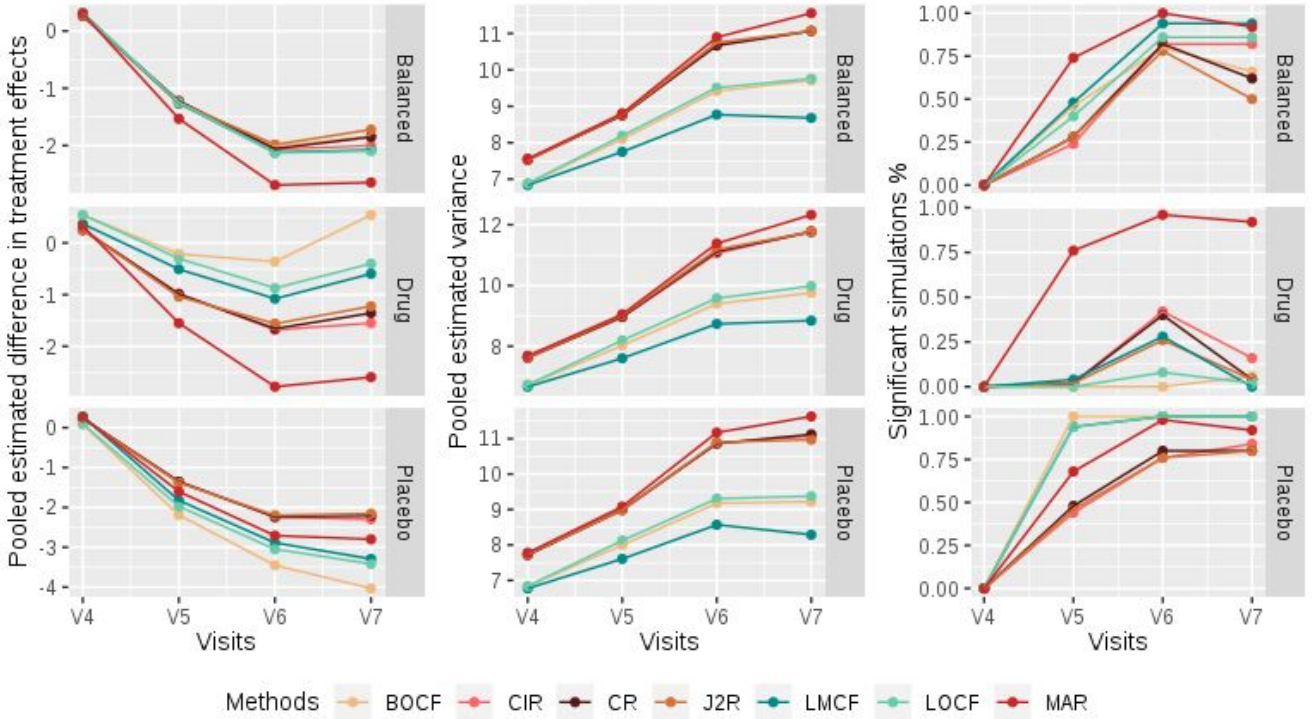
SIMULATION PLANS & APPLICATION

Principal results of the first simulation plan- *effect on an increasing MD%*



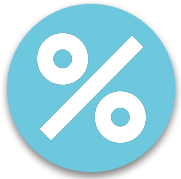
SIMULATION PLANS & APPLICATION

Principal results of the first simulation plan- *impact of distribution - 30%*



SIMULATION PLANS & APPLICATION

First simulation plan main conclusions



J2R and **CR** are **closer** in estimated difference, variance and % significant simulations in the majority of scenarios

→ J2R and CIR **and** 30% MD

SIMULATION PLANS & APPLICATION

Two simulation plans

2 Analyse of the impact of the **sequencing order of imputation** of IEs

DISJOINT

SEQUENTIAL

One IE: one imputation method standard MI, J2R, CIR

Each combination of methods: one **scenario**

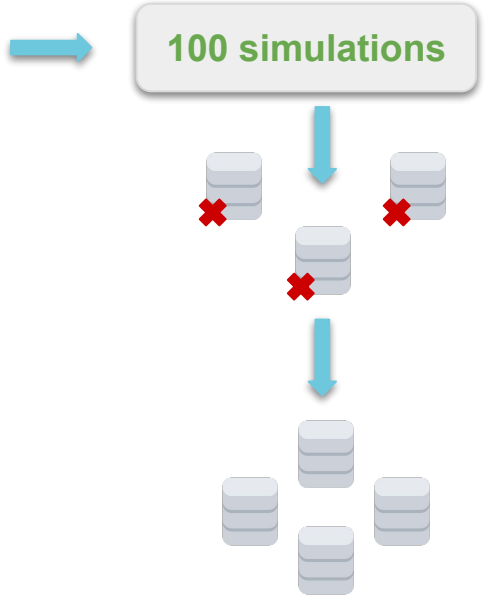
Total: 6 scenarios

→ Recommandations with **clinical relevance**

SIMULATION PLANS & APPLICATION

Principal results of the second simulation plan - *presentation of scenarios*

N° scenario	IE1			IE2		
	Standard MI	J2R	CIR	Standard MI	J2R	CIR
0102	x				x	
0103	x					x
0203		x				x
0201		x		x		
0301			x	x		
0302			x		x	



SIMULATION PLANS & APPLICATION

Principal results of the second simulation plan - *final pooled estimate*

	Imputation order	Estimate V7	% significant
Standard MI & J2R 0102	disjoint	-2.17	80%
	IE1 standard MI- IE2 J2R	-2.19	81%
	IE2 J2R - IE1 standard MI	-2.09	73%
Standard MI & CIR 0103	disjoint	-2.33	90%
	IE1 standard MI- IE2 CIR	-2.31	87%
	IE2 CIR- IE1 standard MI	-2.28	86%
J2R & CIR 0203	disjoint	-1.86	61%
	IE1 J2R - IE2 CIR	-1.85	62%
	IE1 CIR- IE2 J2R	-1.85	60%

SERVIER

ENSAI
École nationale
de la statistique
et de l'analyse
de l'information

CONCLUSION AND PERSPECTIVES

CONCLUSION AND PERSPECTIVES

Recommendations

1. **Effect** of the MD % & disequilibrium of IE distribution between treatment arms

2. **Effect** of the sequential order of imputation if presence of several IEs → need to **define a clinical relevant order** of imputation if possible

CONCLUSION AND PERSPECTIVES

Perspectives

1. Improvement axes:
   - code optimization to reduce time complexity
   - go further in the sensitivity analysis

2. Reuse of the codes

SERVIER

ENSAI
École nationale
de la statistique
et de l'analyse
de l'information

THANKS FOR YOUR ATTENTION

BACK UP SLIDES

Missingness mechanisms

MCAR: missing data of a variable **does not depend** on the variable itself and other study variables

MAR: missing data of a variable **does not depend** on the variable itself (conditional on study variables)

MNAR: missing data of a variable **depends** on the variable itself (conditional on study variables)

MAR and **MNAR** mechanisms

Statistical model - *MMRM model*

Model: $change_{ijk} = baseline_i + therapy_{ij} + (therapy * visit)_{ijk} + \epsilon_{ijk} \Leftrightarrow change = X\beta + \mathcal{E}$

Hypotheses: $\mathcal{E} \sim N(0_n, \Sigma)$

$change \sim N(X\beta, \Sigma)$

→ Use of LS means: obtain the **estimated treatment difference**

Multiple imputation sequential algorithm - *Bayesian predictive regression model*

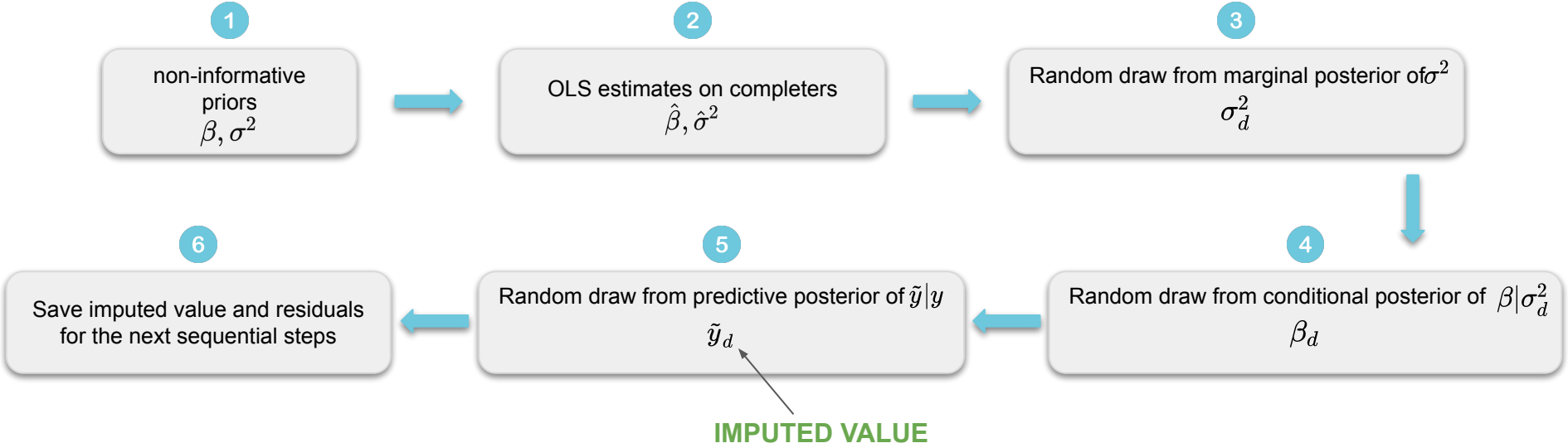
Monotone missing data pattern: sequential imputation

1) Impute values at V4: $change_4 = basval + therapy_4$
2) Impute values at V5: $change_5 = basval + therapy_5 + imputed_4/residual_4$
3) Impute values at V6: $change_6 = basval + therapy_6 + imputed_4/residual_4 + imputed_5/residual_5$
4) Impute values at V7: $change_7 = basval + therapy_6 + imputed_4/residual_4 + \ldots + imputed_6/residual_6$

differences between MNAR methods: variable used for the imputation of visit (t+1)

- J2R and CIR: previous *residuals*
- CR: previous *imputed values*

Multiple imputation sequential algorithm - *Steps to impute one visit measurement*

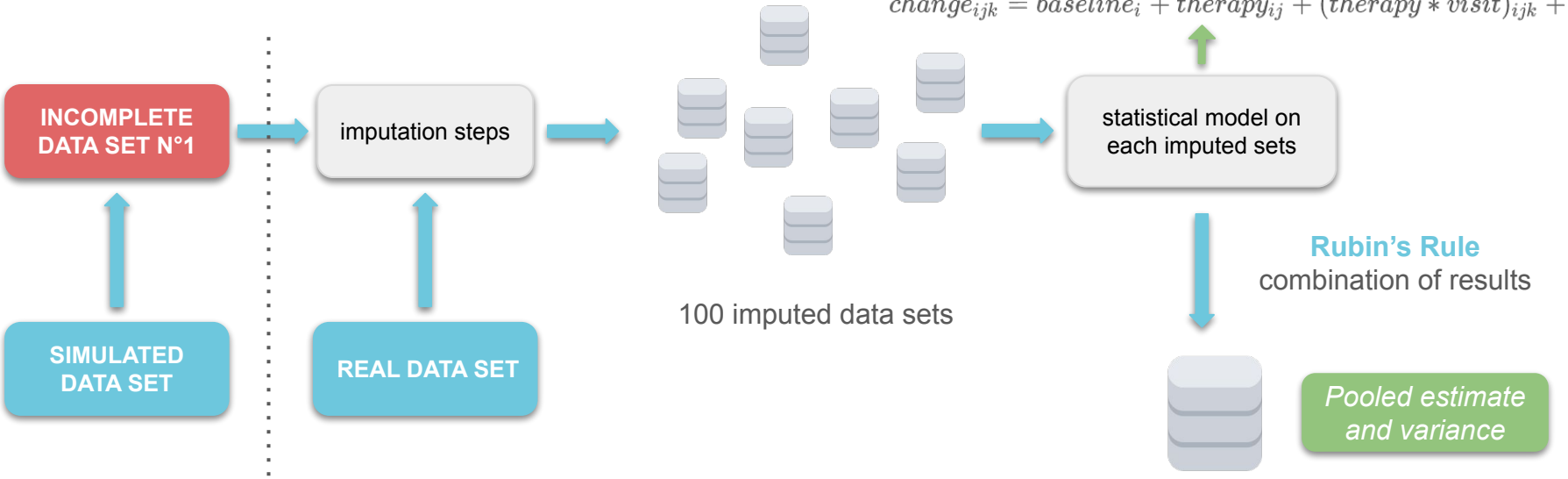


reiterate **2)** to **5)** for each visit (for exemple for V5 visit, the model for imputed value is:

$$change_5 = basval + therapy_5 + imputed_4/residual_4$$

reiterate this imputation algorithm to create **100 different imputed datasets**

Pool of all 100 results



imputation, statistical model application and pool of results for each of the **scenarios** and for the **several simulations**

Rubin’s Rule - pooling of results

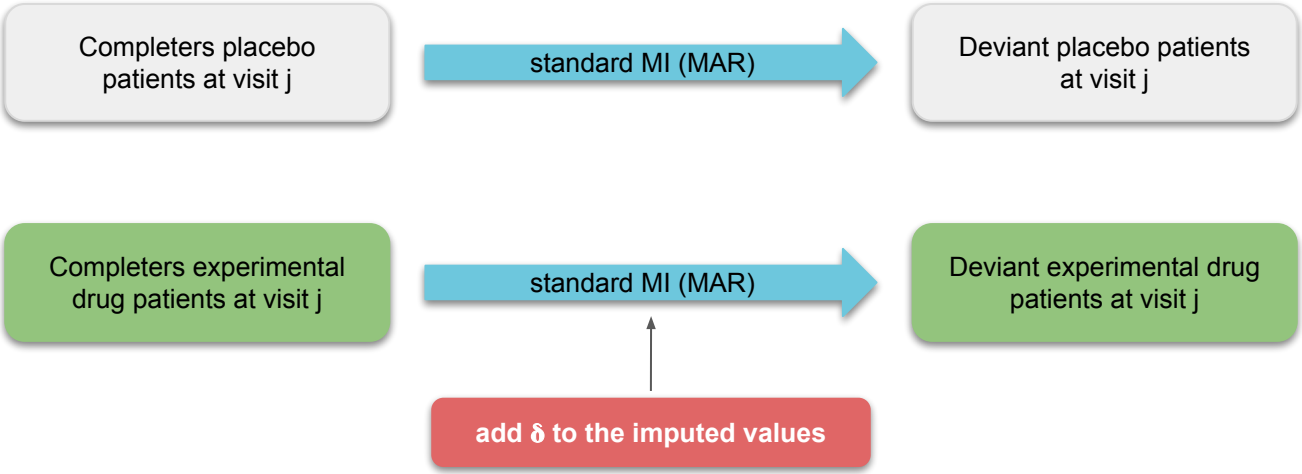
Pooling of the **m** different estimates: $\tilde{\theta} = \frac{1}{m}(\sum_{i=1}^{m} \hat{\theta}_i)$

Several steps to pool the estimated variance: $V_W = \frac{1}{m}(\sum_{i=1}^{m} SE_i^2)$

$$V_B = \frac{1}{m-1}\Sigma_{i=1}^{m}(\hat{\theta}_i - \tilde{\theta})^2$$

$$V_T = V_W + (1 + \frac{1}{m})V_B$$

Delta-adjustment theory



SERVIER

ENSAI
École nationale
de la statistique
et de l'analyse
de l'information

SENSITIVITY ANALYSIS ON A REAL DATA SET

SENSITIVITY ANALYSIS ON REAL DATA SET

Literature review on sensitivity analysis

Use of an intern Servier research tool (R Shiny app)

No concluding findings because recent concerns & subject

Final version of the ICH-E9 Addendum about sensitivity analysis **not released yet**

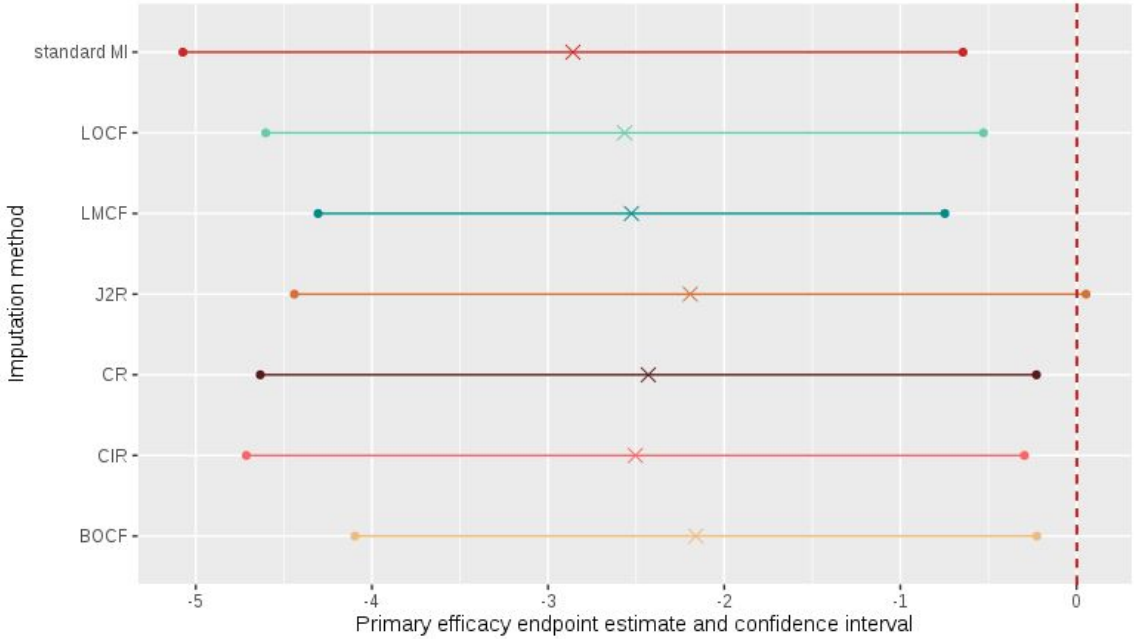
TIPPING POINT

SENSITIVITY ANALYSIS ON REAL DATA SET

Application of all selected imputation methods - *effect on the estimate*

Visit	Estimate (se) p-value
V4	0.47 (0.82) *0.57*
V5	-1.38 (1.04) *0.18*
V6	-2.47 (1.06) *0.022*
V7	-2.83 (1.17) *0.017*

26 % MD



SENSITIVITY ANALYSIS ON REAL DATA SET

Tipping point theory- *objectives*

Aim: assess how severe departures from the initial assumption must be in order to overturn conclusions of the primary analysis

Helps to **determine the robustness of results**

SENSITIVITY ANALYSIS ON REAL DATA SET

Tipping point theory *- based on delta-adjustment method*

DELTA ADJUSTMENT

- penalize the chosen treatment arm imputation by a **mean** value (e.g. 1) → **DELTA**
- apply the statistical model and the pool of results over the different imputed sets

TIPPING POINT

- apply **progressive** delta-adjustment with a delta value: from 0 to the **TIPPING POINT**
- **TIPPING POINT:** when the results are overturned → loss of significance

SENSITIVITY ANALYSIS ON REAL DATA SET

Tipping point results - *find the tipping point for this study*