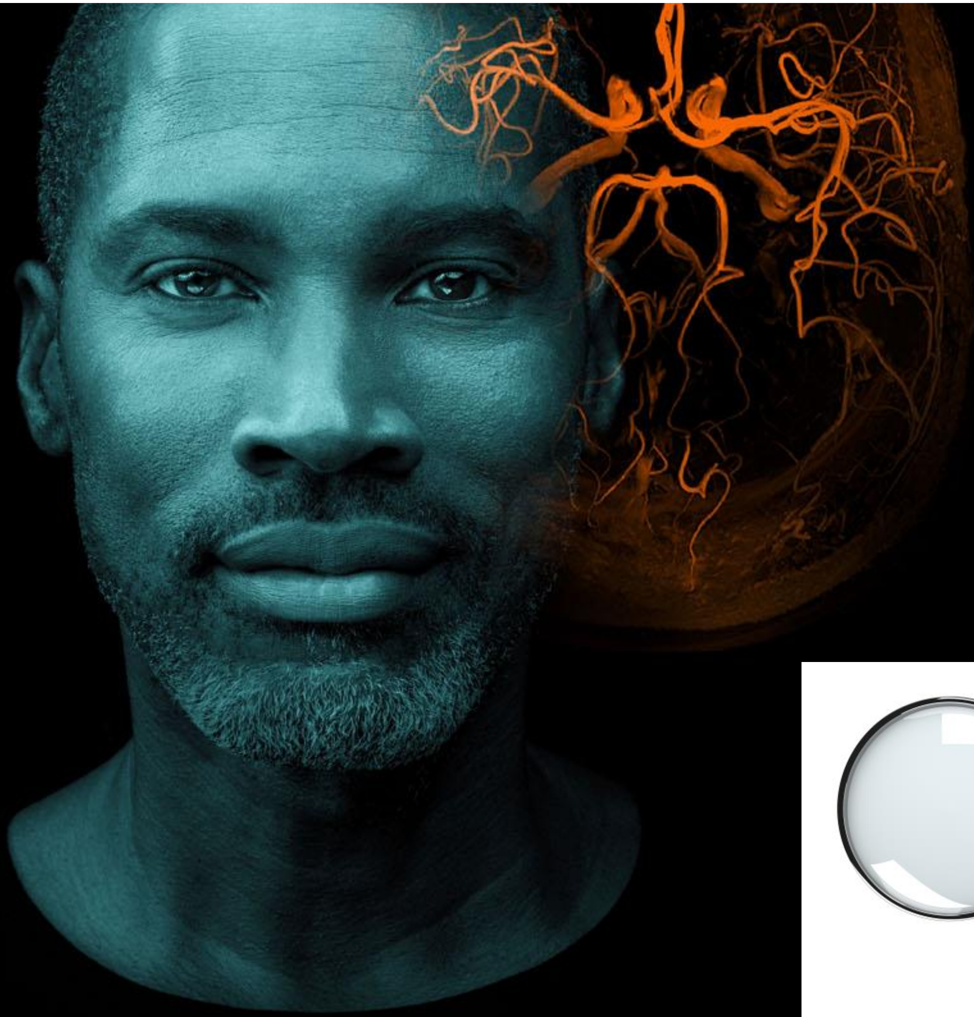
SIEMENS Healthineers

A Case Study: The Adventure of the Missing Data



Presented By:
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Thanks to Siemens Healthineers leadership, colleagues, and staff for their support of this work.

2024
Siemens Healthineers

Introductions

Dr. Viral Panchal

- Dr. Viral Panchal earned his DrPH in Biostatistics from Jiann-Ping Hsu College of Public Health at Georgia Southern University, where he also completed his MPH. Prior to that, he received his Bachelor of Medicine and Surgery (MBBS) from Maharaja Sayajirao University, India.
- After completing his education, he completed his postdoctoral fellowship at the Medical College of Georgia. He then held the role of biostatistician at Duke University Medical Center before serving as an assistant professor and later as an adjunct professor of biostatistics at the University of North Carolina, Wilmington.
- Currently, he works as a staff biostatistician at Siemens Healthineers, where he leads and supports point-of-care projects in preclinical biostatistics.

Dr. Ryan Butterfield

- Dr. Ryan Butterfield resides in St. Augustine, FL with family. On a personal note, he enjoys time with his family and golfing and reading as much as having little kids and his wife permits.
- His educational experiences resulted in a BS in Biomathematics and MPH in Biostatistics from Loma Linda University, an MBA from Jacksonville University, and a DrPH in Biostatistics from Georgia Southern University, where he was a BASS Fellow.
- Since graduating, he has worked as a Biostatistician in academia, hospital/clinical/University settings, varying levels of government (Local, State, Federal), and at several multi-international corporations at varying levels including 3M, Johnson & Johnson, and Edwards Lifesciences.
- He currently is a Senior Director of Clinical Biostatistics at Siemens Healthineers, where his team supports all stages of product development from R&D through Market entry.

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  - Design, Outcomes, Population, etc.
- Study Execution
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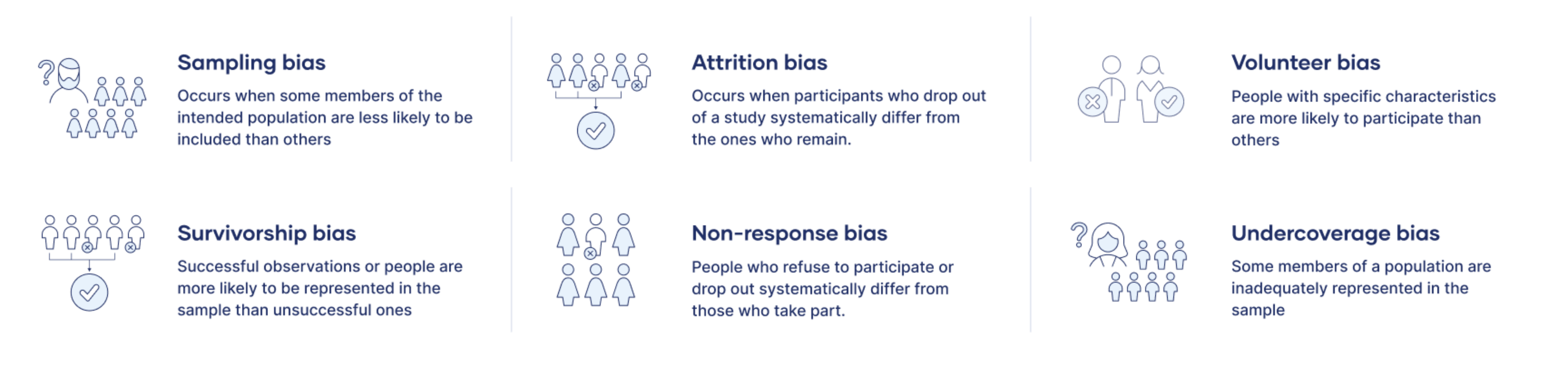
  - Selection Bias
- Introduction to Missing Data
  - How to assess missing data
  - Specific Missing Data Issues with this study
  - Types of missing data observed
    - MCAR, MAR, MNAR, Reasons
    - Based on Diagnostic Accuracy
- Discussion - Forensic Review: What Could Have Been Done?
- Conclusions
- Q&A

The Facts: Study Design

- Longitudinal Cohort Study – multiple timepoints and sample categories
- A test device compared to adjudicated confirmatory diagnostic outcome as agreed upon by a panel of Physicians
- Primary outcome is Diagnostic Accuracy i.e. Sensitivity, Specificity, PPV, NPV and supporting inferential statistics
- Approximately 30 sites – Emergency Departments
- Expected Sample Size: n =1500

The Facts: Study Execution

- Challenges to be Examined:
  - Execution was from Spring 2020 – Fall 2022
  - As a result of the study being conducted during COVID there were issues with:
    - Slow enrollment
    - Low Prevalence
    - Inconsistent Provider Participation of the study
  - As a result, there were Protocol revisions due to these issues, which possibly resulted in:
    - Potential Selection bias – from protocol changes
    - Attrition and Missing Data – due to COVID and the natural clinical progression of disease and treatment response
  - And it is these two challenges we will explore in this talk.



Challenge 1: The Influence of Selection Bias

- What kind of selection Bias do we have?
- KEY Question:
  - Is there Consistency of outcome and performance for these various scenarios?
- Descriptive comparison –
  - Are revision populations similar?
  - Is attrition over time an issue?

Population Comparison

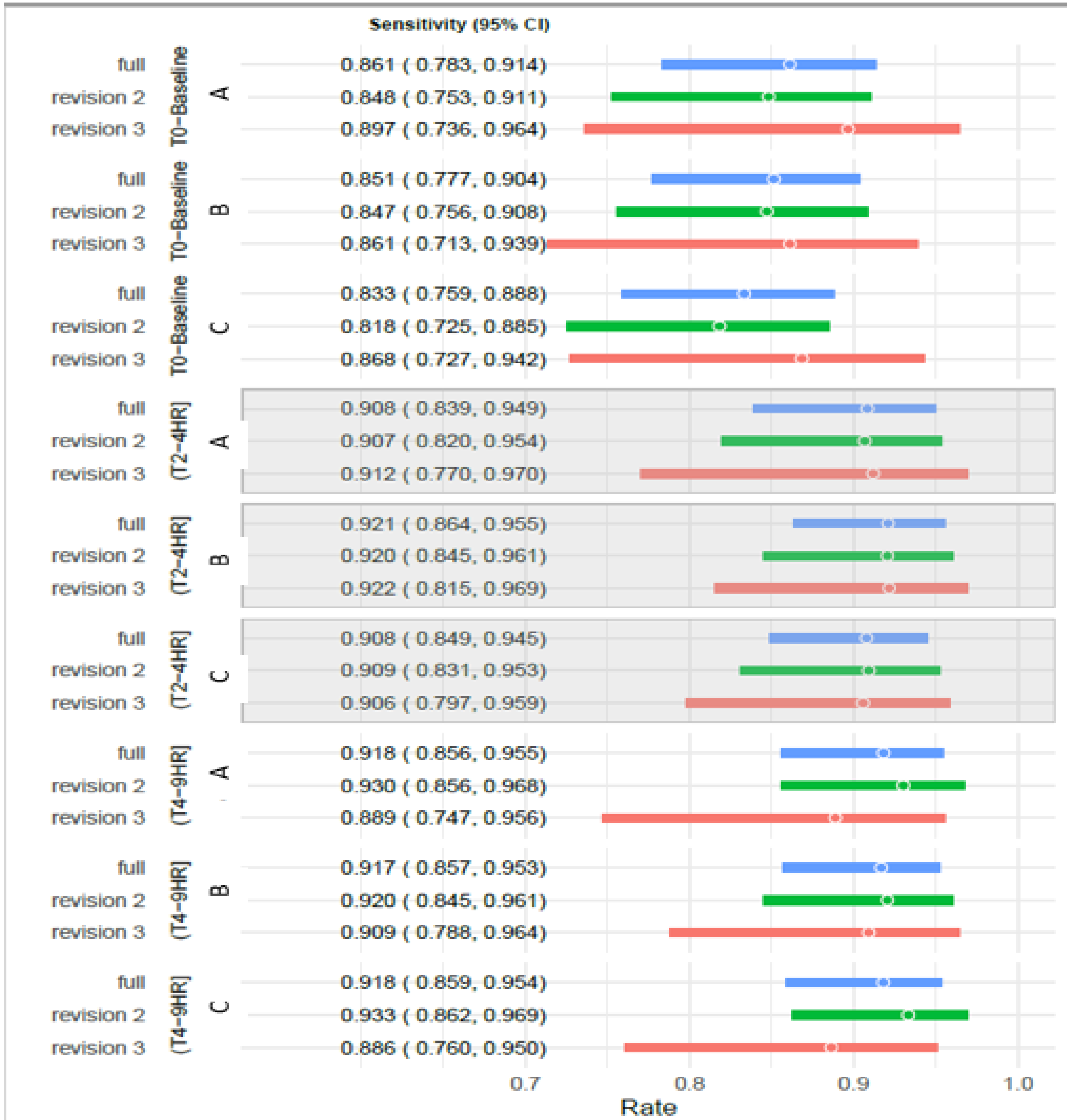
		Revision 2	Revision 3	Overall
Disease outcome				
	Present	10.3%	10.7%	10.4%
	Absent	89.7%	89.3%	89.6%
Age (Years)				
	Mean (SD)	56.5 (14.3)	57.2 (13.7)	56.7 (14.1)
	Min-Max	23.0 – 89.0	23.0 – 89.0	23.0 – 89.0
Race				
	White	53.6%	50.9%	52.6%
	Black or African American	41.8%	41.4%	41.6%
	Asian	0.7%	0.9%	0.8%
	Other	1.3%	1.2%	1.3%
	Unknown	2.6%	5.5%	3.7%
Hypertension				
	Yes	70.6%	69.3%	70.1%
	No	28.2%	30.5%	29%
	Unknown	1.2%	0.2%	0.9%
Diabetes				
	Yes	34.1%	33.2%	33.8%
	No	64.8%	66.1%	65.2%
	Unknown	1.1%	0.7%	1%
Lipid Disorder				
	Yes	42.7%	45.5%	43.7%
	No	55.2%	54.1%	54.8%
	Unknown	2.1%	0.4%	1.4%

Prevalence of Missing Results by Timepoint, Revision, and Sample Type

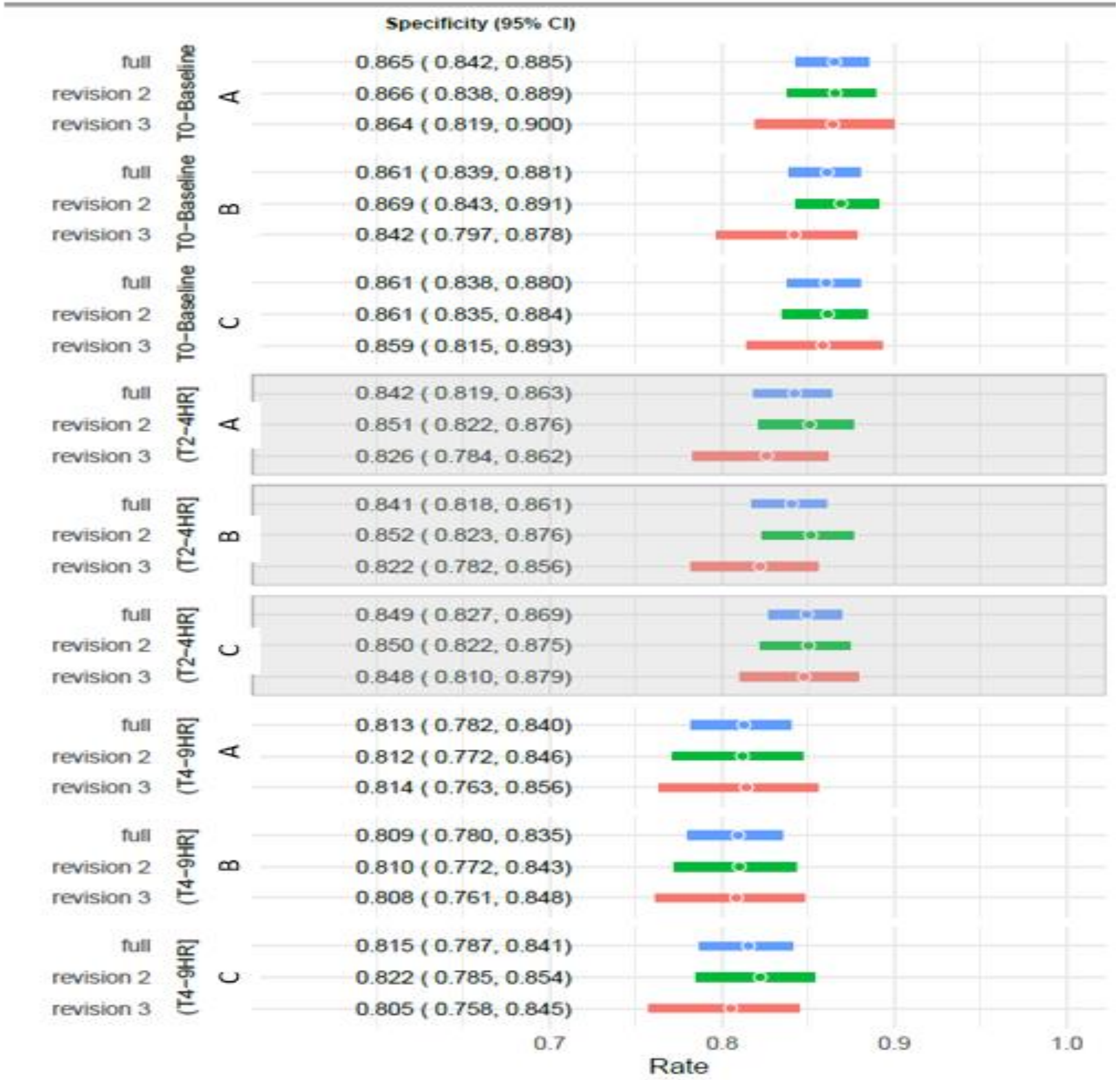
	Revision 2 & 3			Revision 2			Revision 3		
	% Missing (Sample A)	**% Missing (Sample B)**	**% Missing (Sample C)**	**% Missing (Sample A)**	**% Missing (Sample B)**	**% Missing (Sample C)**	**% Missing (Sample A)**	**% Missing (Sample B)**	**% Missing (Sample C)**
T0									
Overall	28%	22%	23%	19%	13%	13%	45%	38%	39%
T2-4 HR									
Overall	25%	18%	17%	23%	18%	18%	29%	16%	15%
T4-9 HR									
Overall	46%	39%	39%	47%	41%	41%	45%	36%	36%

- Do we see different prevalence of missing results between Revisions? Over time? Between Sample types?

Performance Between Revisions

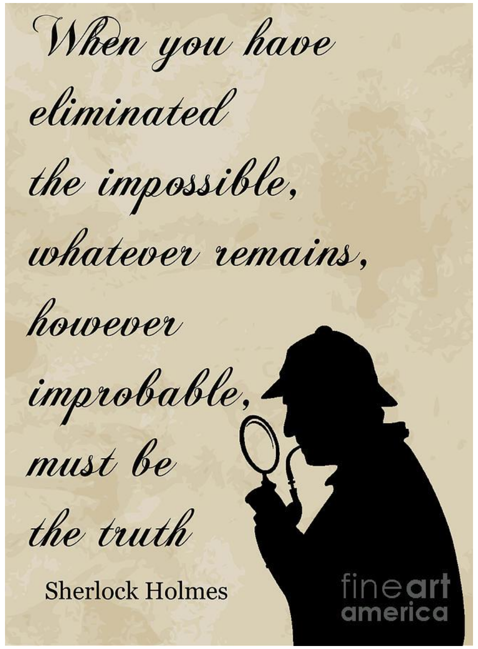


Performance Between Revisions

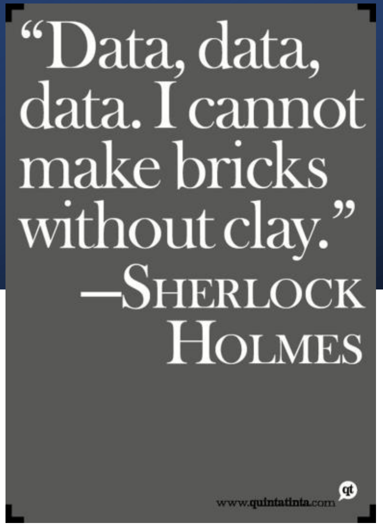


Challenge 1: Conclusion

- Similar population characteristics between the revisions
- Consistent clinical performance between the revisions
- Minimal systematic bias from the revision change



Challenge 2: Missing Data



Identify if the reasons for Missing Data for missing are Systematic and/or Random

Are reasons causal or correlational?

Evaluate missing data patterns

Are they Arbitrary or Systematic?

Then Evaluate Base Assumptions regarding Mechanism(s) for missing:

MCAR Assumption

MAR Assumption

MNAR Assumption

Based on this Evaluation an imputation approach is selected, and then appropriate comparisons are made

Carefully select which statistical processes will lead to the best insights

Challenge 2: The Missing Data

	Revision 2 & 3			Revision 2			Revision 3		
	% Missing (Sample A)	**% Missing (Sample B)**	**% Missing (Sample C)**	**% Missing (Sample A)**	**% Missing (Sample B)**	**% Missing (Sample C)**	**% Missing (Sample A)**	**% Missing (Sample B)**	**% Missing (Sample C)**
T0									
Overall	28%	22%	23%	19%	13%	13%	45%	38%	39%
T2-4 HR									
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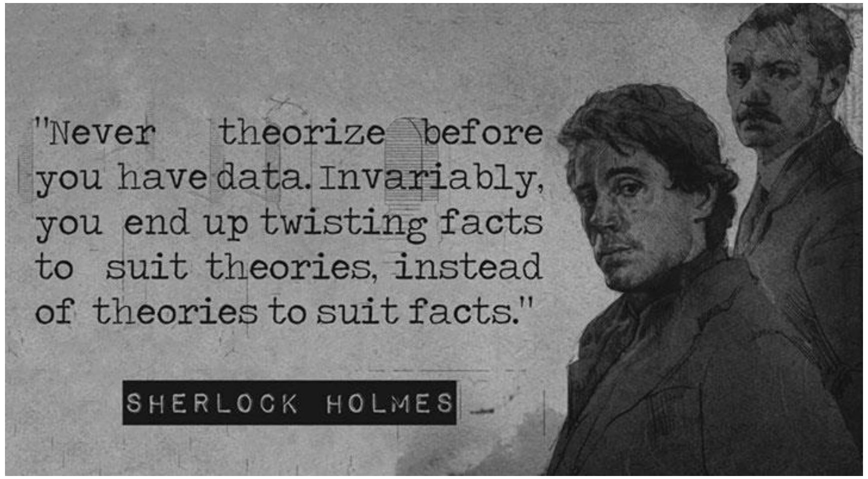
T4-9 HR									
Overall	46%	39%	39%	47%	41%	41%	45%	36%	36%

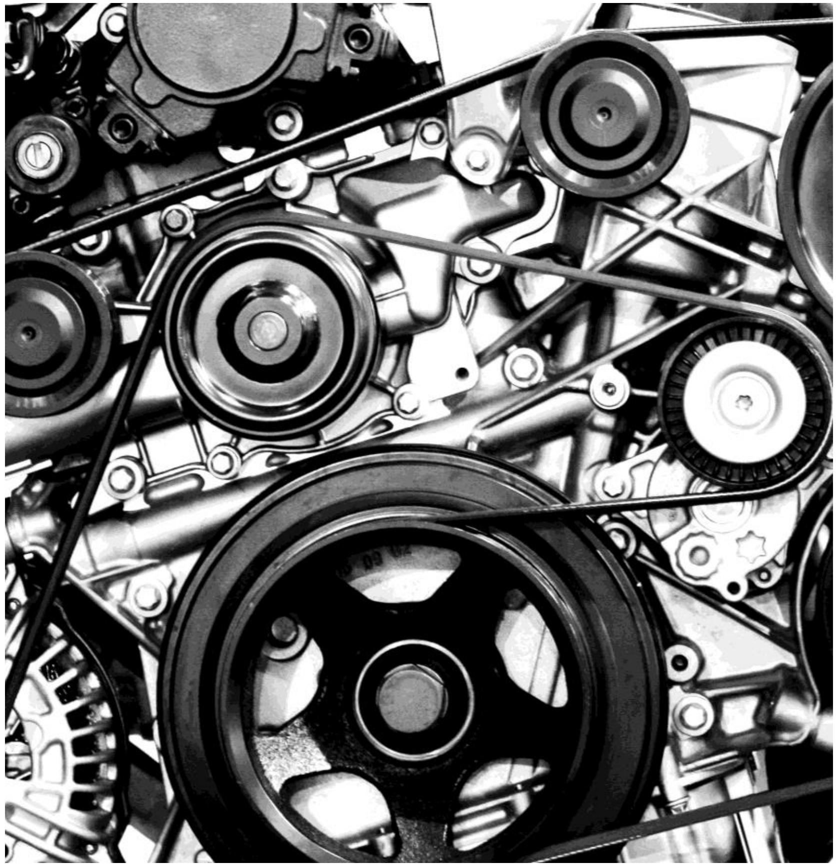
Challenge 2: The Missing Data

- Reasons for missing data
  - Clinical environment (COVID)
  - Sample collection
  - Revision change
  - Attrition over time
  - Clinical pathway
  - Operational difficulties



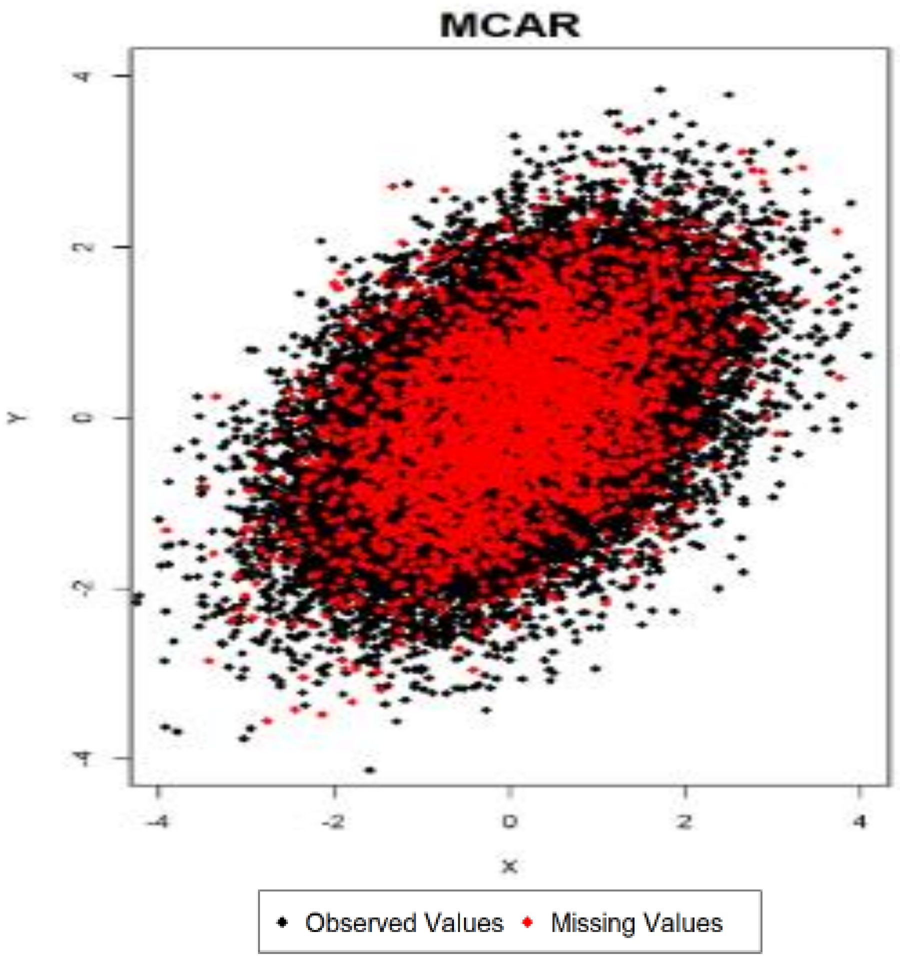
How to Assess Missing Data?

- Concepts of MCAR, MAR, and MNAR
  - Start with the likelihood of a data point being missing (Rubin, 1976)
    - i.e. what is the *missing data mechanism or response mechanism*?
- What are the missing data patterns?
- Are there systematic factors (i.e. study execution, sample collection difficulties)



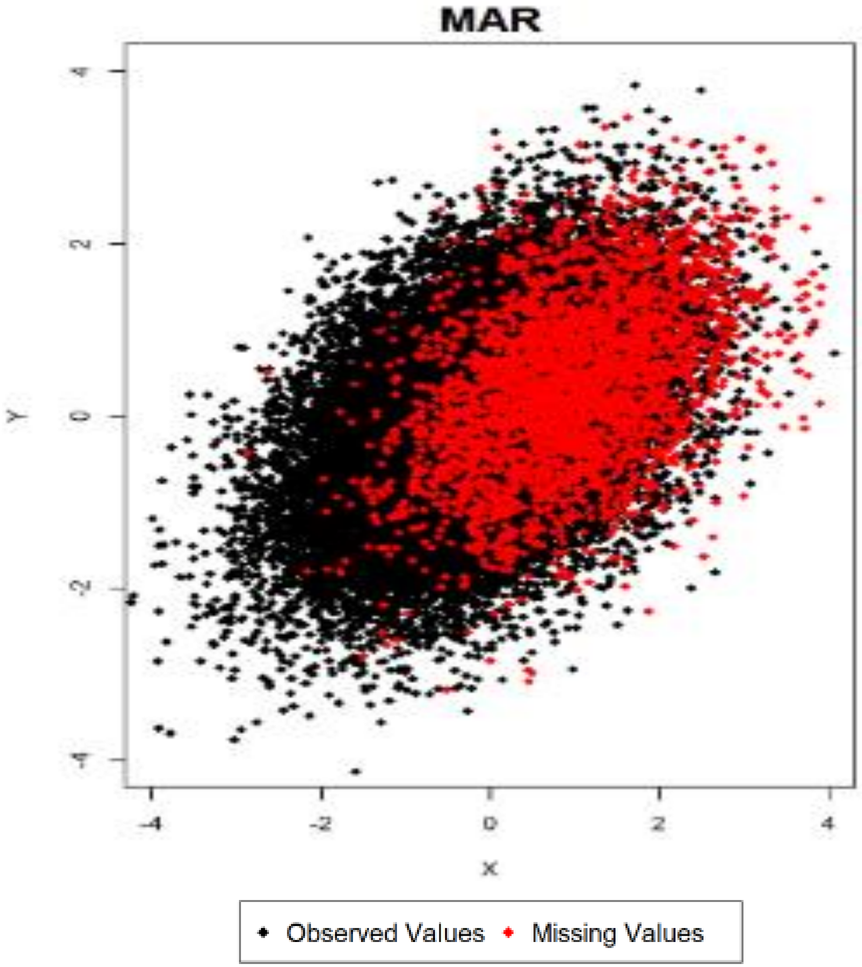
MCAR

- Missingness is independent of both the observed data and unobserved data.



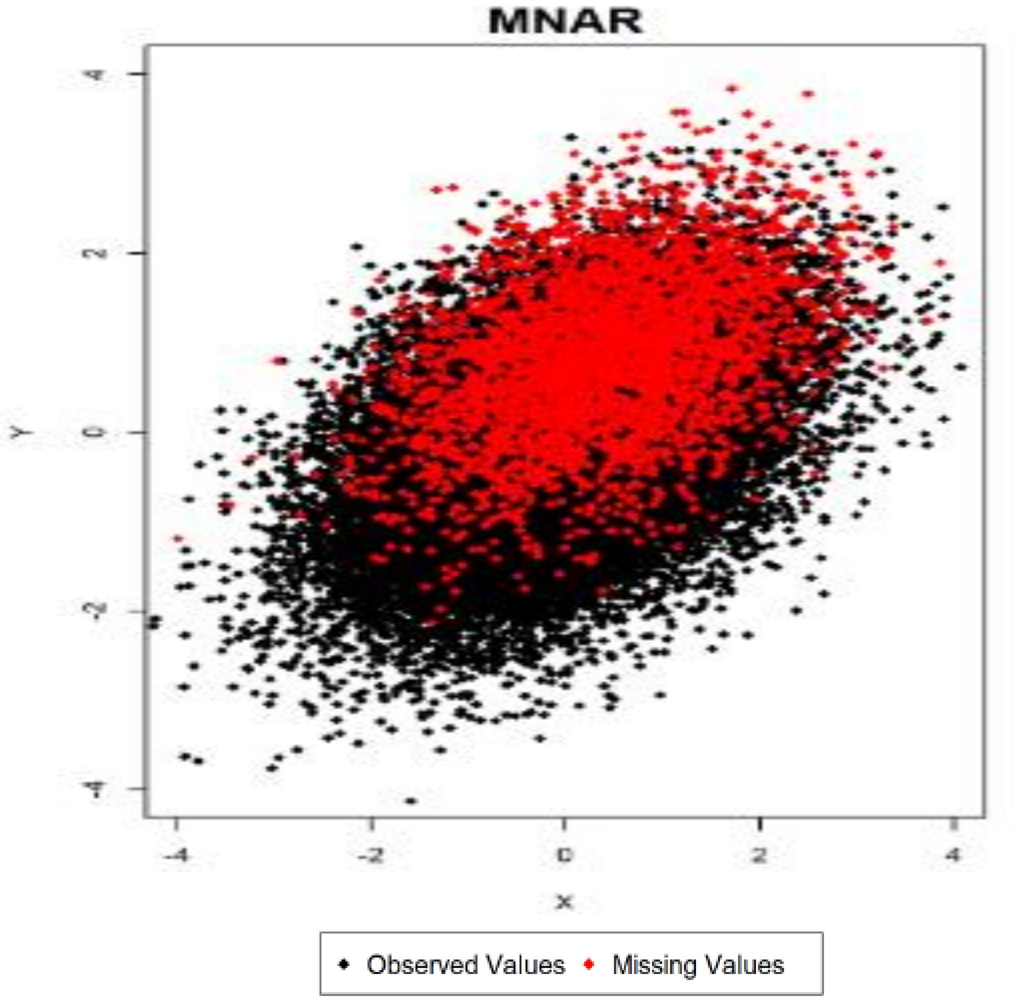
MAR

- Missingness depends on the observed data values but does not depend on the unobserved data values.

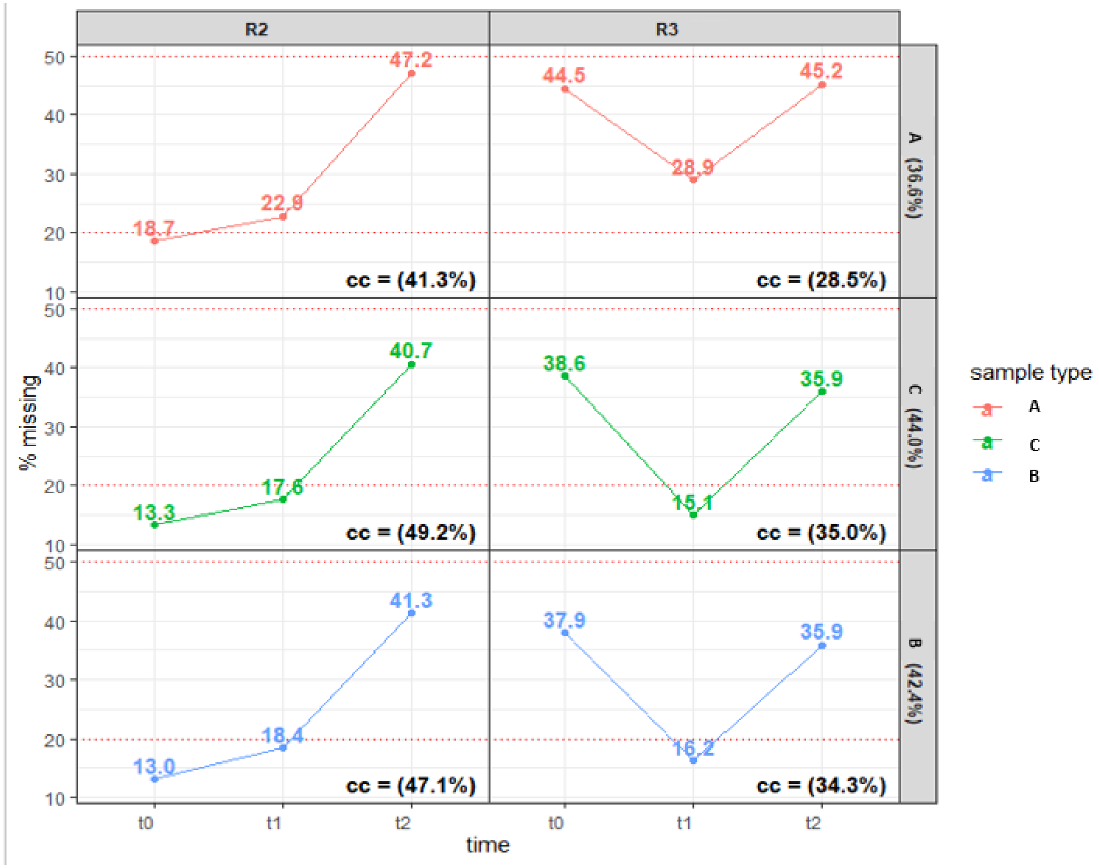


MNAR

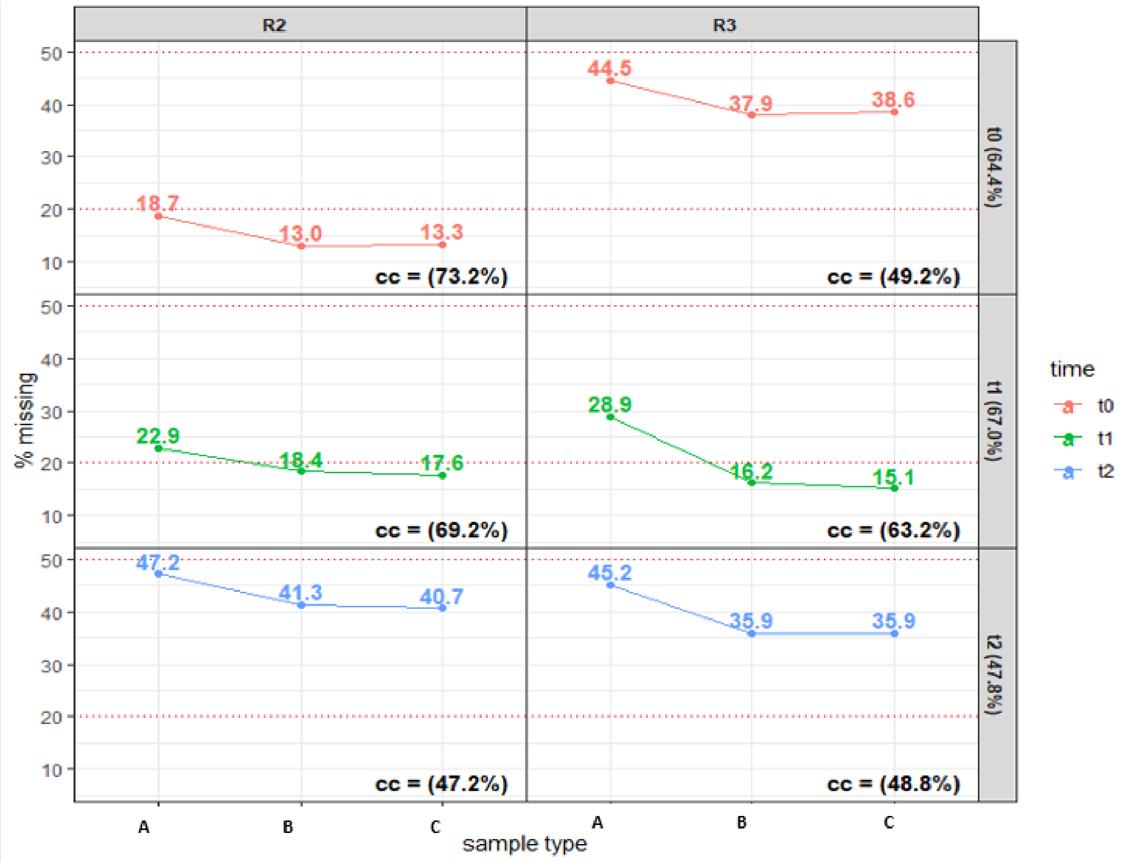
- Missingness depends on the unobserved data values.



% Missing, % CC of Sample Types and Time By Revision



Note: cc= complete cases



Note: cc= complete cases

Sample Type:

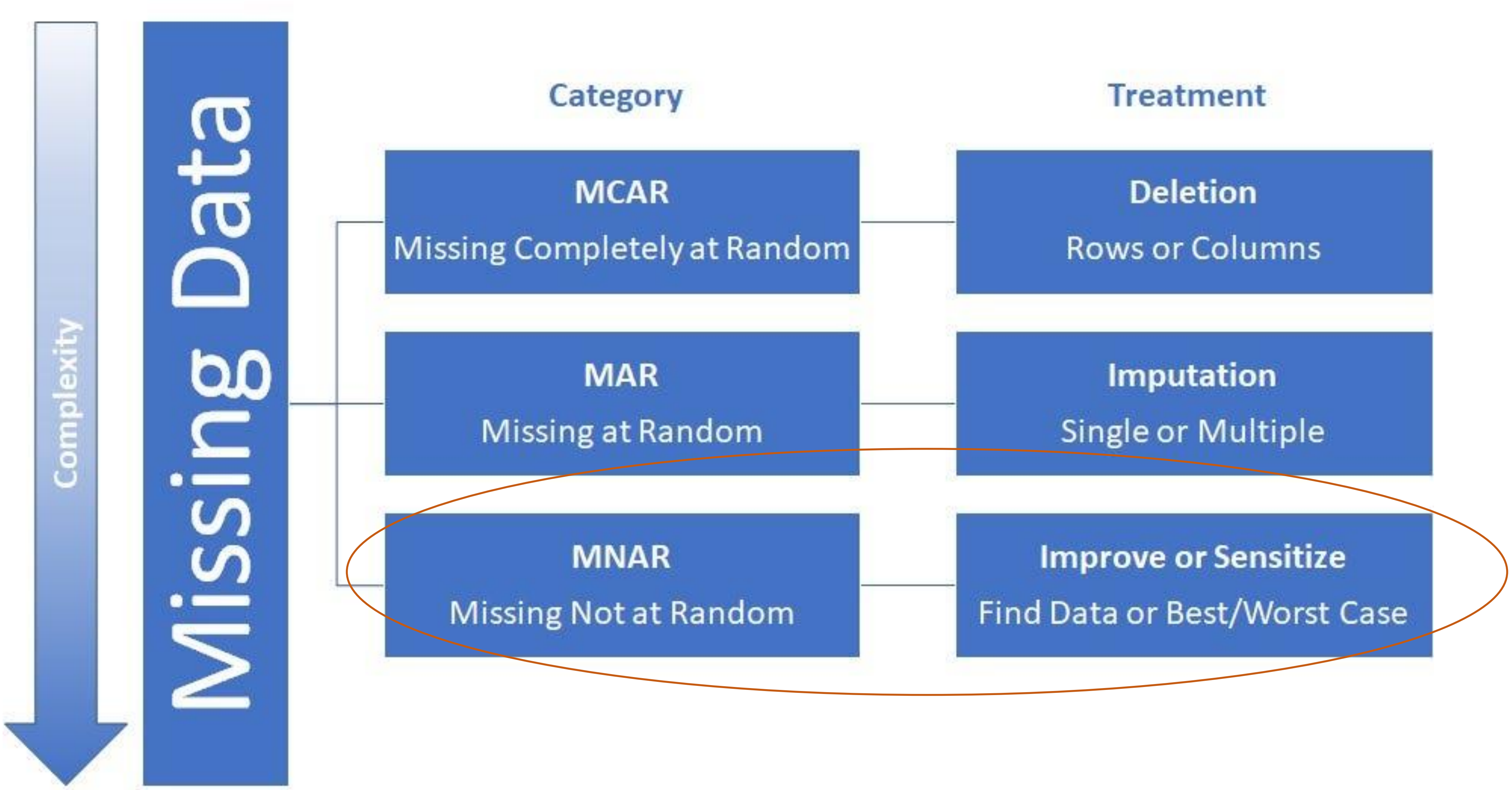
- Shapes are vastly different by revision
- Within revision, shapes and magnitude across time are consistent by sample type

Time:

- Trend is similar to sample type
- However, the magnitude of displacement varies across time.
- Consequence of Rev 3 is evident in upper righthand corner

"Completeness" was the most consistent across sample types at R2 baseline

What to do…


Complexity
Missing Data
Category
Treatment
MCAR
Missing Completely at Random
Deletion
Rows or Columns
MAR
Missing at Random
Imputation
Single or Multiple
MNAR
Missing Not at Random
Improve or Sensitize
Find Data or Best/Worst Case

Missing Data Pattern – ITD Population

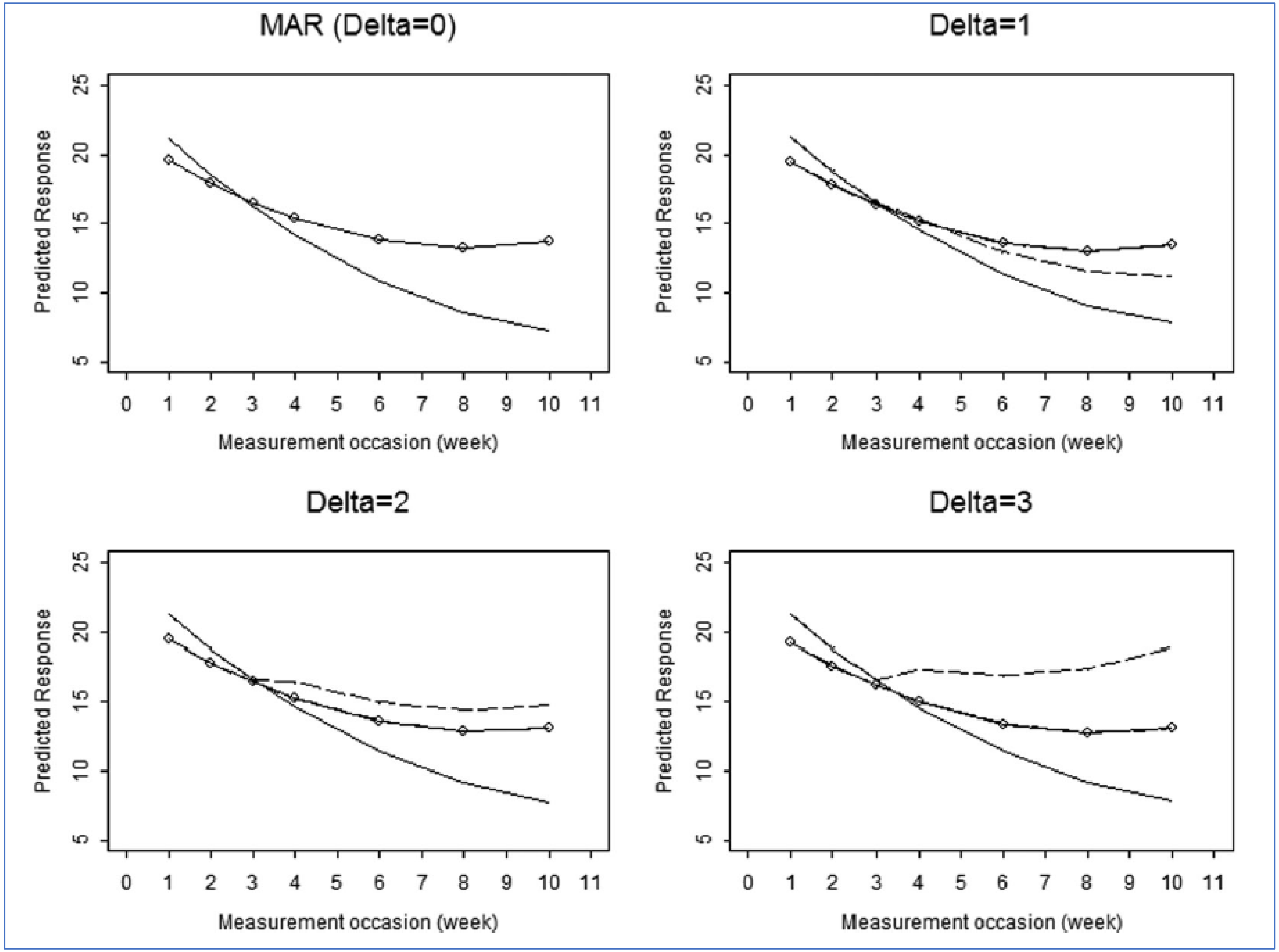
Obs	Group	A_T0	A_T2_4	A_T4_9	B_T0	B_T2_4	B_T4_9	C_T0	C_T2_4	C_T4_9	Freq	Percent
1	1	X	X	X	X	X	X	X	X	X	466	30.56
2	28	X	X	.	X	X	.	X	X	.	214	14.03
3	88	.	X	X	.	X	X	.	X	X	98	6.43
4	71	X	.	.	X	.	.	X	.	.	65	4.26
5	24	X	X	.	X	X	X	X	X	X	42	2.75
6	122	.	.	.	X	X	X	X	X	X	39	2.56
7	109	.	X	.	.	X	.	.	X	.	29	1.90
8	47	X	.	X	X	X	X	X	X	X	25	1.64
9	124	.	.	.	X	X	.	X	X	.	25	1.64
10	102	.	X	.	X	X	.	X	X	.	24	1.57
11	141	O	O	O	O	O	O	O	O	O	24	1.57
12	65	X	.	.	X	X	.	X	X	.	22	1.44
13	82	.	X	X	X	X	X	X	X	X	22	1.44
14	132	.	.	.	.	X	X	.	X	X	21	1.38
15	8	X	X	X	X	X	.	X	X	.	17	1.11
16	52	X	.	X	X	.	X	X	.	X	17	1.11
17	37	X	X	.	X	.	.	X	.	.	15	0.98
18	105	.	X	.	.	X	X	.	X	X	14	0.92
19	117	.	.	X	.	X	X	.	X	X	14	0.92
20	129	.	.	.	X	.	.	X	.	.	14	0.92
21	43	X	X	.	.	X	.	.	X	.	11	0.72
…												
134	127	.	.	.	X	.	X	.	.	X	1	0.07
135	128	.	.	.	X	.	X	.	.	.	1	0.07
136	130	.	.	.	X	.	.	.	.	X	1	0.07
137	133	.	.	.	.	X	X	.	.	.	1	0.07
138	135	.	.	.	.	X	.	.	.	.	1	0.07
139	136	.	.	.	.	.	X	X	X	X	1	0.07
140	137	.	.	.	.	.	X	.	.	X	1	0.07
141	138	.	.	.	.	.	.	X	X	.	1	0.07

X = the variable is observed. • or O = the variable is missing.

- Only 466 (30.56%) of Patients are complete-cases (sample types and timing).
- Only 24(1.6%) of Patients are complete-missing due to PDs.
- Arbitrary missing data pattern
- Reasons for missing – Systematic and Random.

MNAR

<u>Example of Delta-Adjustment Strategy for the Hamilton Depression Study</u>.
-Solid lines: completers;
-dash lines: dropouts at fourth week;
-dots: experimental group;
-circles: control group.



MNAR

- We performed a sensitivity analysis assuming MNAR data <u>to determine the bounds of the imputation.</u>
- We assumed two scenarios for the missing observations assuming missing not-at-random.
  - Scenario 1: Missing values were higher than the observed values. (Positive shift: +1.14)
  - Scenario 2: Missing values were lower than the observed values. (Negative shift: -1.14)
- The robustness of the estimates was assessed by comparing the performance estimates between available data and imputed data under MAR and MNAR assumptions.

MNAR – Shift Justification

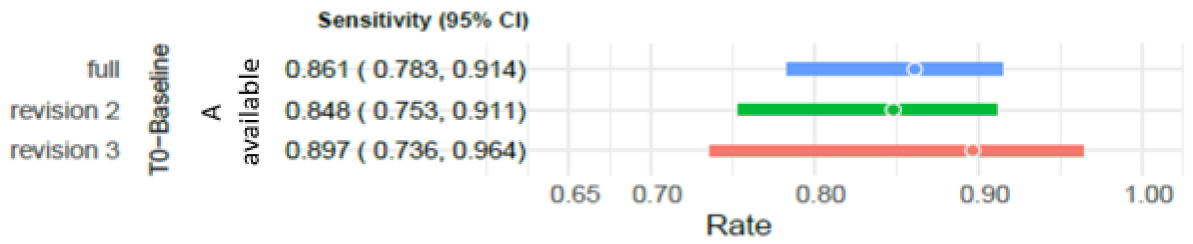
Difference in Median Results for All Sample Types and Time Points

Time Point	Sample Type	δ
T0-Baseline	A	1.3
	B	1.35
	C	1.5
T2-4HR	A	1.55
	B	1
	C	1.6
T4-9HR	A	0.775
	B	0.1
	C	1.05

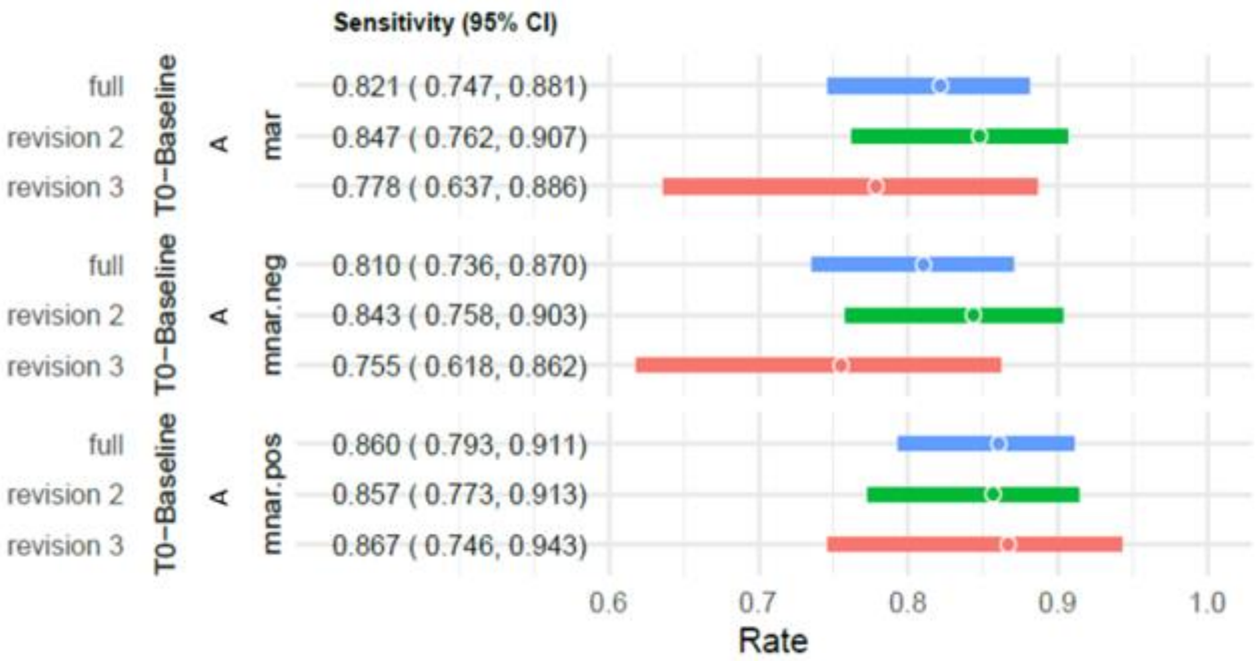
Results For Challenge 2: Missing Data

Comparison of Sensitivity Estimates – **T0-Baseline**

Available Data



Imputed Data

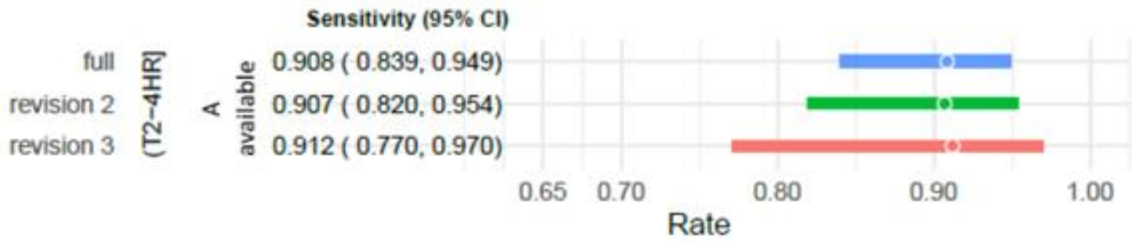


Note: 'O' on the bar is the point estimate; full = dataset including data from revisions 2 and 3; available = dataset with available results; mar = data imputed under MAR; mnar.neg = data imputed under MNAR with negative shift; mnar.pos = data imputed under MNAR with positive shift.

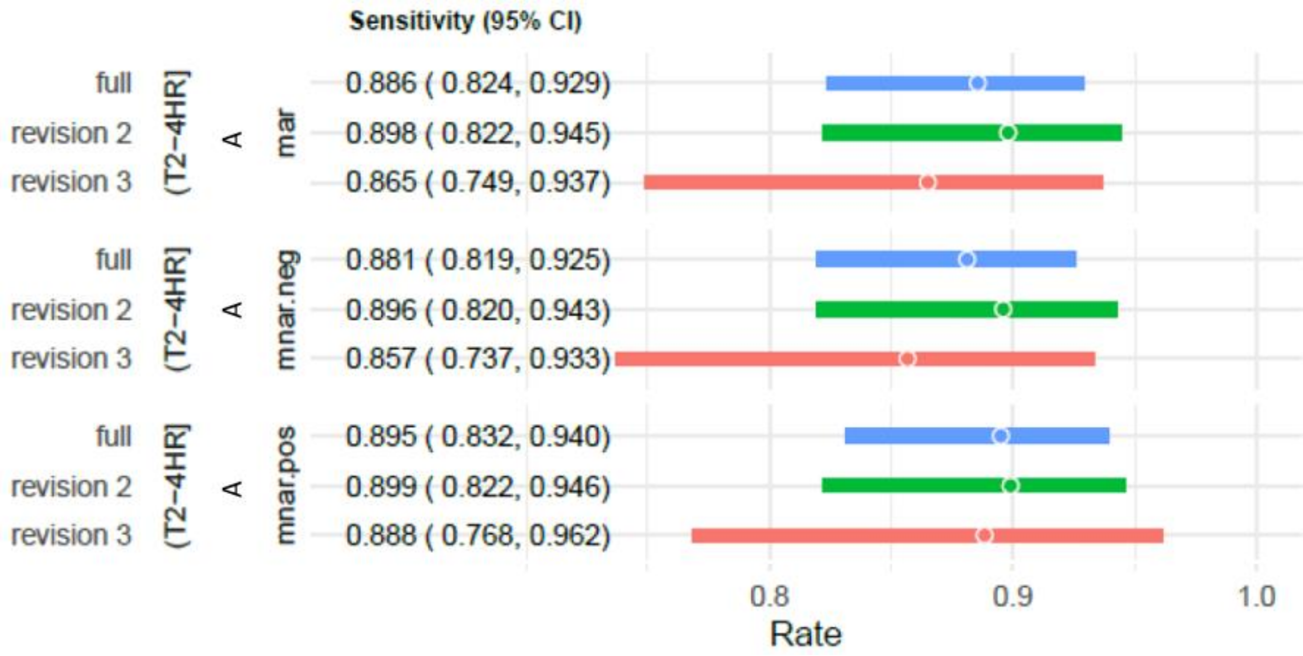
Results For Challenge 2: Missing Data

Comparison of Sensitivity Estimates – **T2-4HR**

Available Data



Imputed Data



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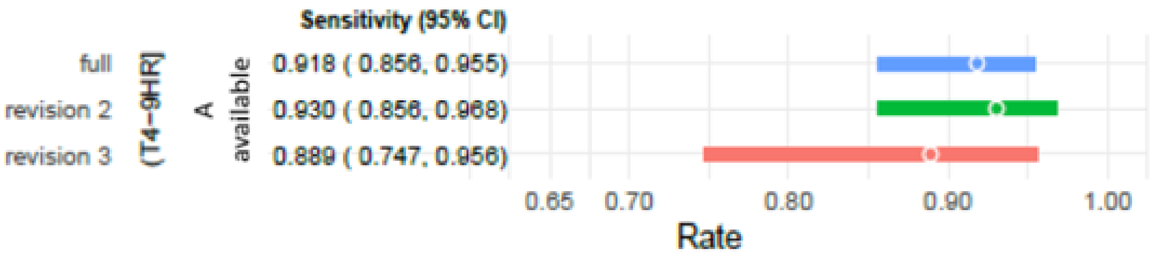
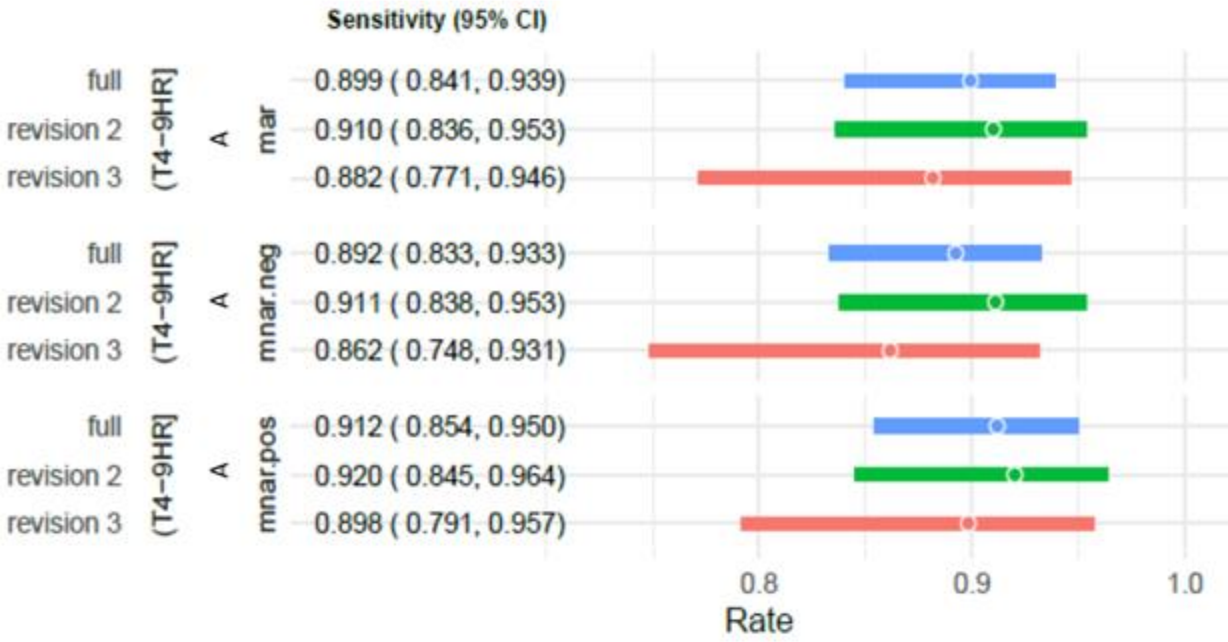
Results For Challenge 2: Missing Data

Comparison of Sensitivity Estimates – **T4-9 HR**

Available Data



Imputed Data



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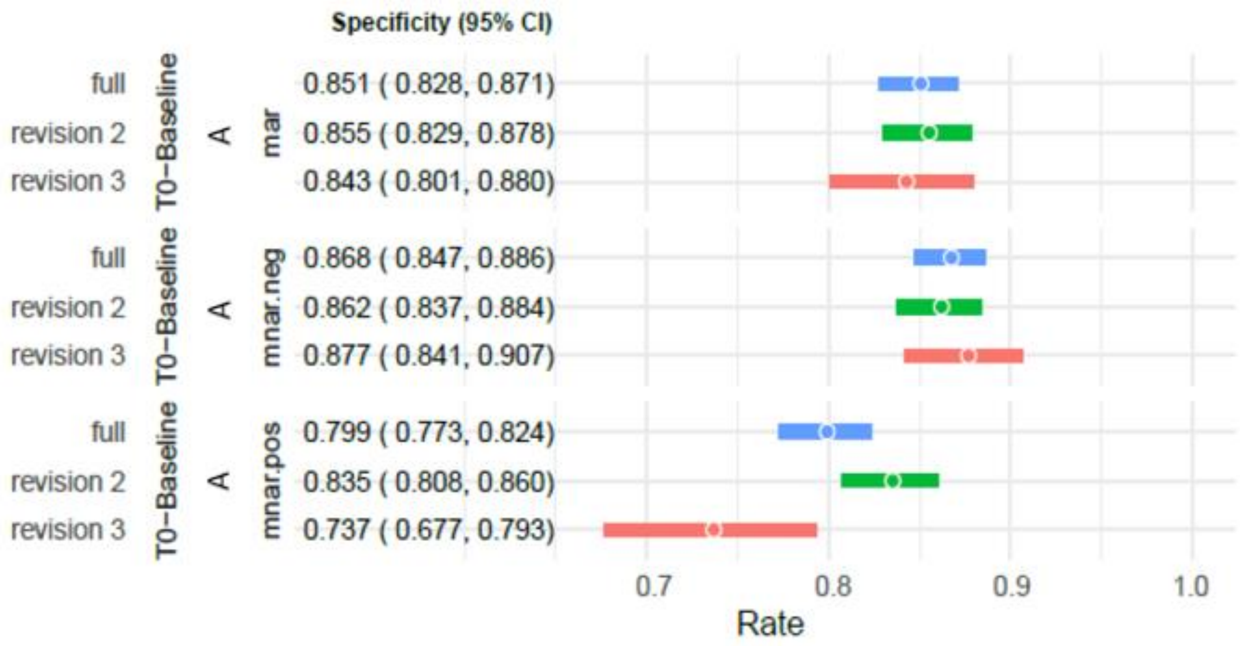
Results For Challenge 2: Missing Data

Comparison of Specificity Estimates – **T0-Baseline**

Available Data

Imputed Data



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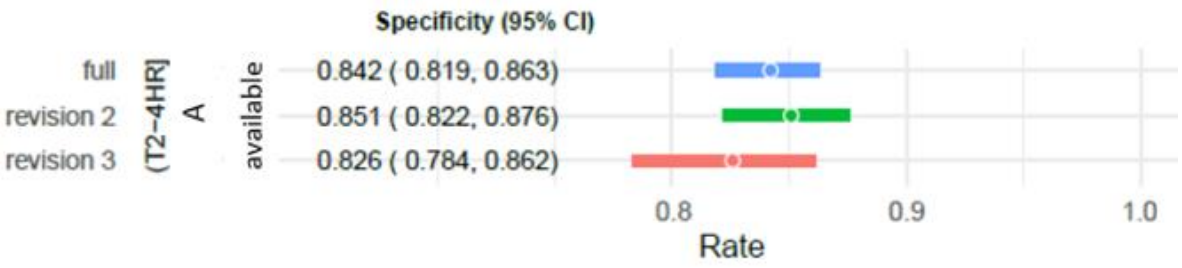
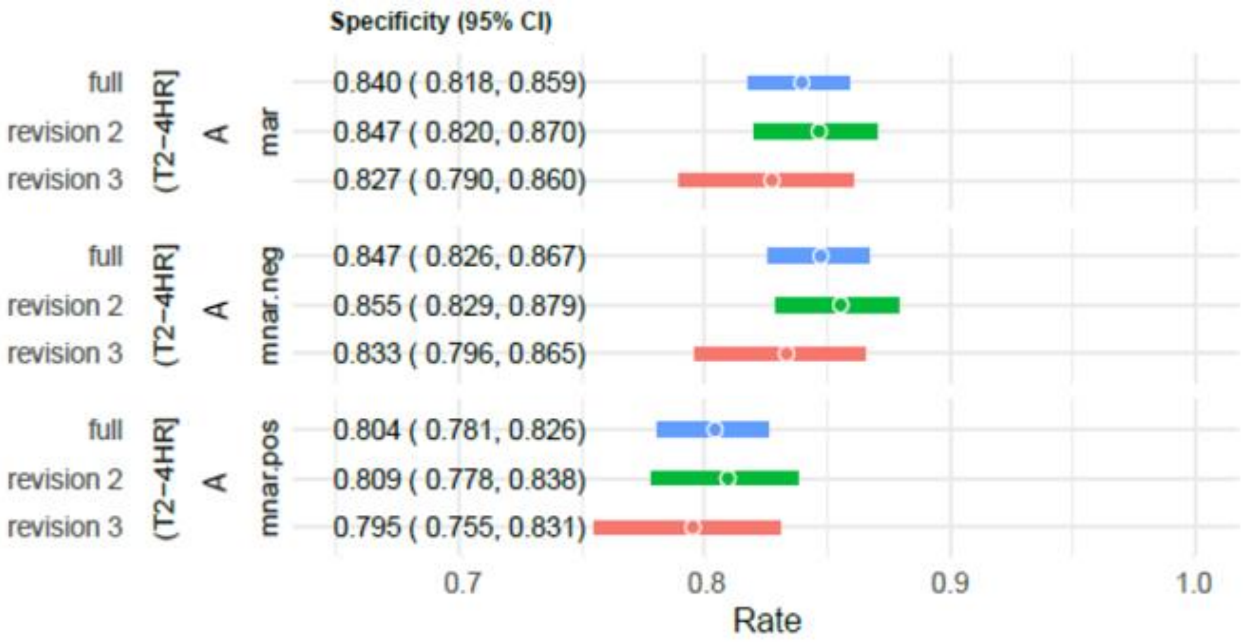
Results For Challenge 2: Missing Data

Comparison of Specificity Estimates – **T2-4 HR**

Available Data



Imputed Data



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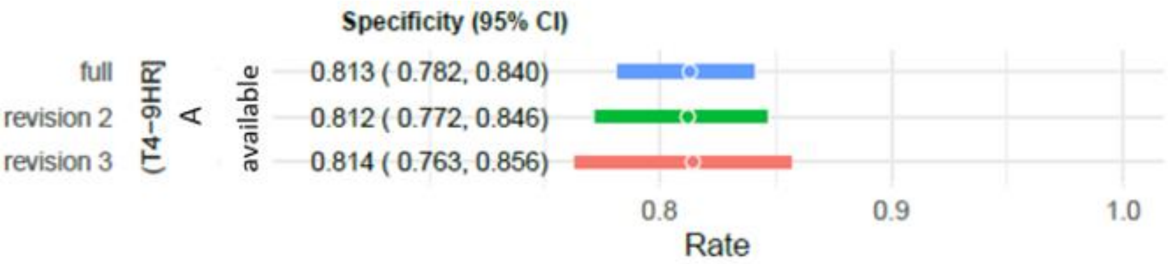
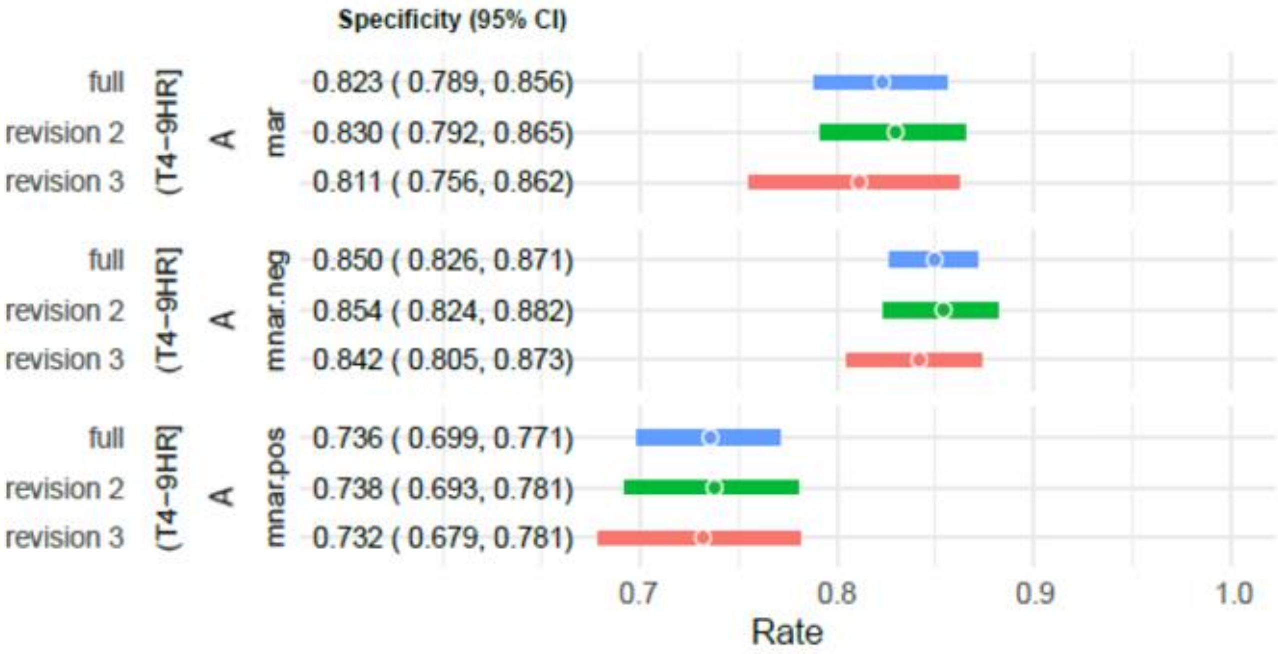
Results For Challenge 2: Missing Data

Comparison of Specificity Estimates – **T4-9HR**

Available Data



Imputed Data



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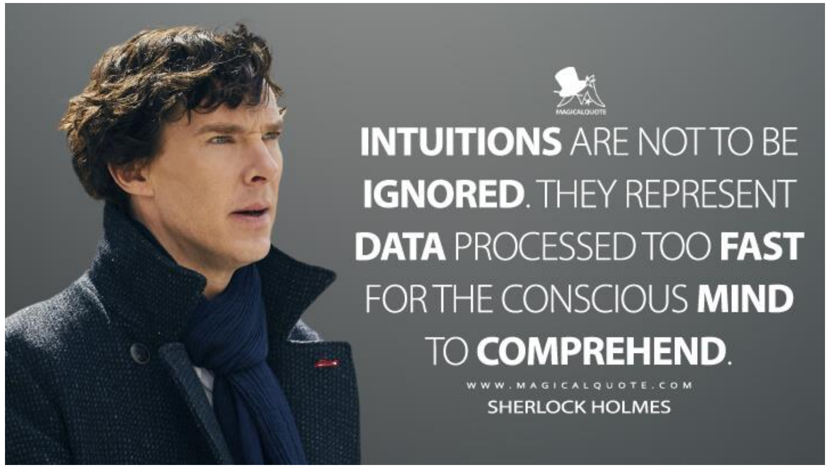
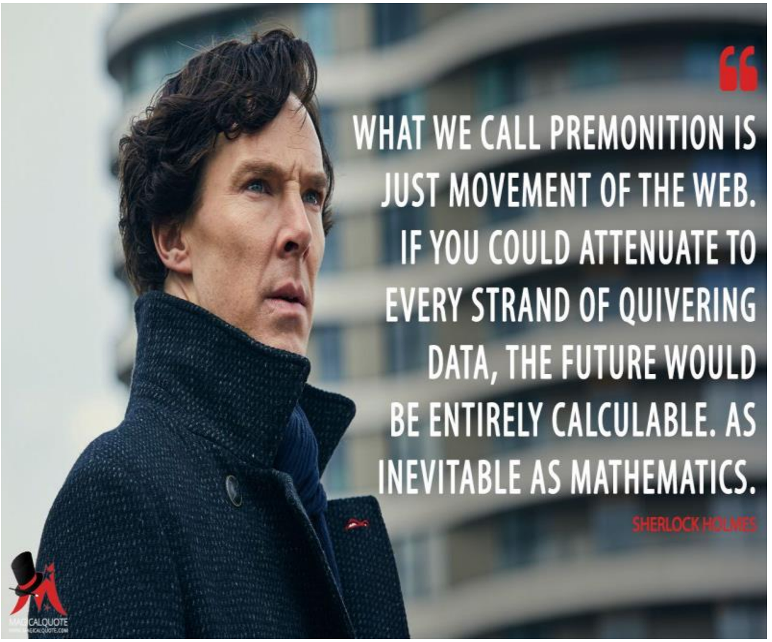
Challenge 2: Conclusion

- Robustness of the performance estimates in response to departures from underlying assumptions (MAR and MNAR).
- There was found to be consistency between the observed data and the imputed scenarios, even with the underlying MNAR assumptions.



Forensic Review: Lessons Learned



- Selection Bias
  - If not preemptively accounted for, then this can produce issues with generalizability and representativeness of the intended population.
  - Frequent and clear communication with the regulatory body helps to minimize this risk.
- Missing Data
  - Pre-specification of missing data handling plan is a must, alignment on this approach with regulatory agencies is just best practice.
    - Challenges within imputation are varying but having specifics as to which analysis variables and design elements need to be accounted for is a crucial step to success.
  - The best treatment for missing data is to prevent having missing data.

Q&A

10/28/2024

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