Beyond MICE in RWE

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Single Day Events

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Disclaimer

Agenda

- RWE Concept & Challenges
- Imputation Workflow & Approaches
- Classification of missing data
- About MICE
- What is Beyond MICE?

Real World Evidence

Randomized trials are like test-driving a car on a closed track.

Real-World Evidence (RWE) is driving it through real traffic - potholes, detours, warning lights, and all.

By analyzing routine healthcare data, RWE shows how treatments actually perform in everyday clinical practice. The catch? Real-world data often comes with missing pieces - like a dashboard where half the indicators don’t light up.

Imputing missing data is one of RWE’s biggest challenges: necessary to keep the car moving, but tricky to do without accidentally changing the destination. Getting it right is key to turning real-world chaos into reliable, decision-ready evidence.

Workflow Diagram for RWE Imputation

STEP	OBJECTIVE	TOOLS/METHODS
Explore Missingness	Identify extent and pattern	Heatmaps, summary statistics
Identify Mechanism	Classify MCAR/MAR/MNAR	Little’s test, correlations
Select Method	Choose appropriate imputation	MICE, ML-based
Diagnostics	Validate imputation quality	Distribution checks
Sensitivity Analysis	Test robustness	Tipping-point analysis

Classify – MCAR, MAR or MNAR

MCAR
(Missing Completely At Random)

P(missing) is unrelated to any variable – observed or missing

Lab tech forgot to record 10 random samples

→ Little's MCAR test

MAR
(Missing At Random)

P(missing) depends on observed variables only

Older, heavier patients are less likely to have BMI recorded

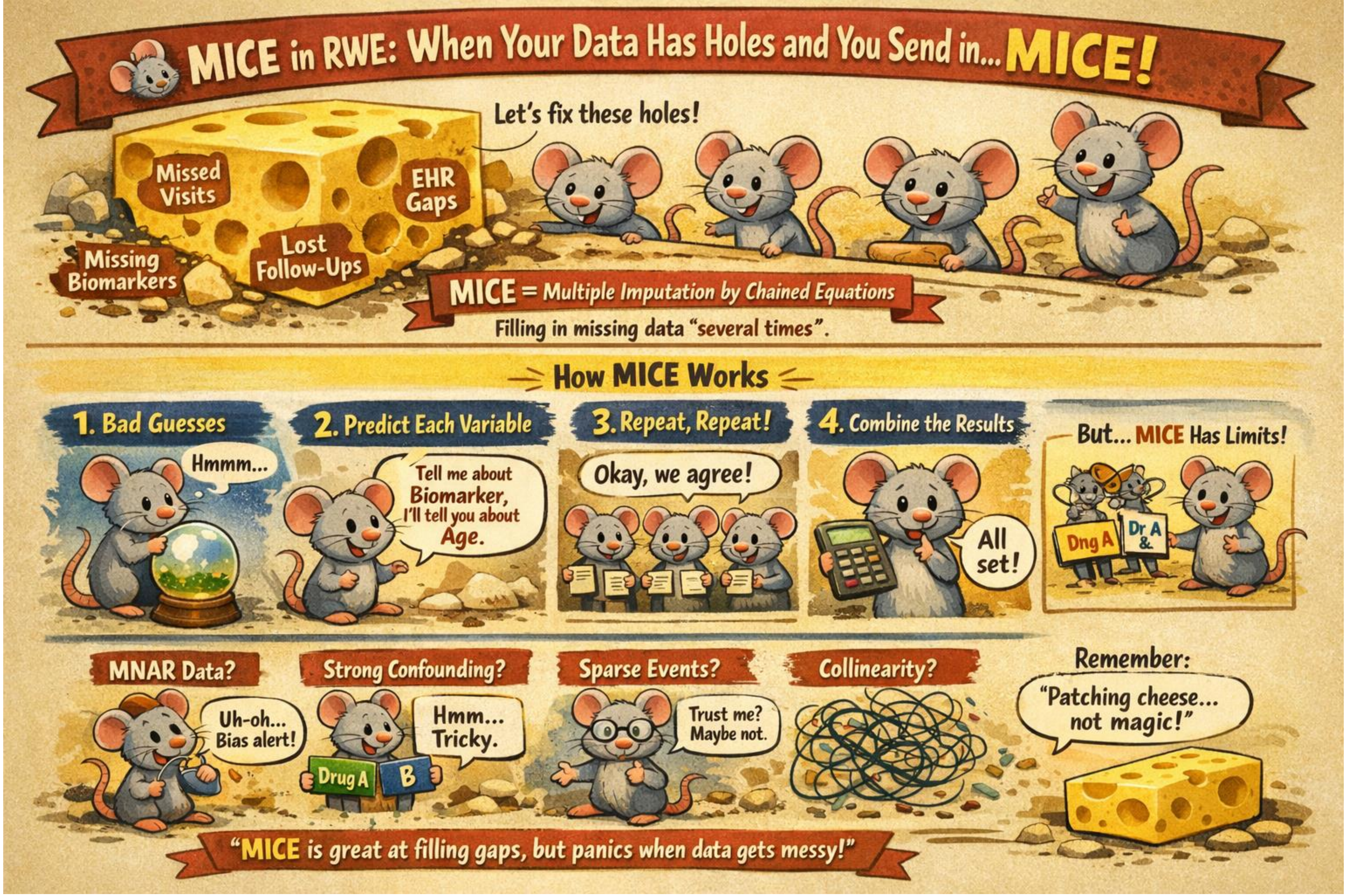
→ Logistic Regression

MNAR
(Missing Not At Random)

P(missing) depends on the missing value itself

Patients with high HbA1c skip tests

→ Sensitivity Analysis



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What is Beyond MICE?

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MICE: Bayesian – RF – PMM

Initialize

Fill missing values with means

→

Iterate Col 1

Regress on all other cols

→

Iterate Col 2

Regress on all other cols

→

Iterate Col k

Regress on all other cols

→

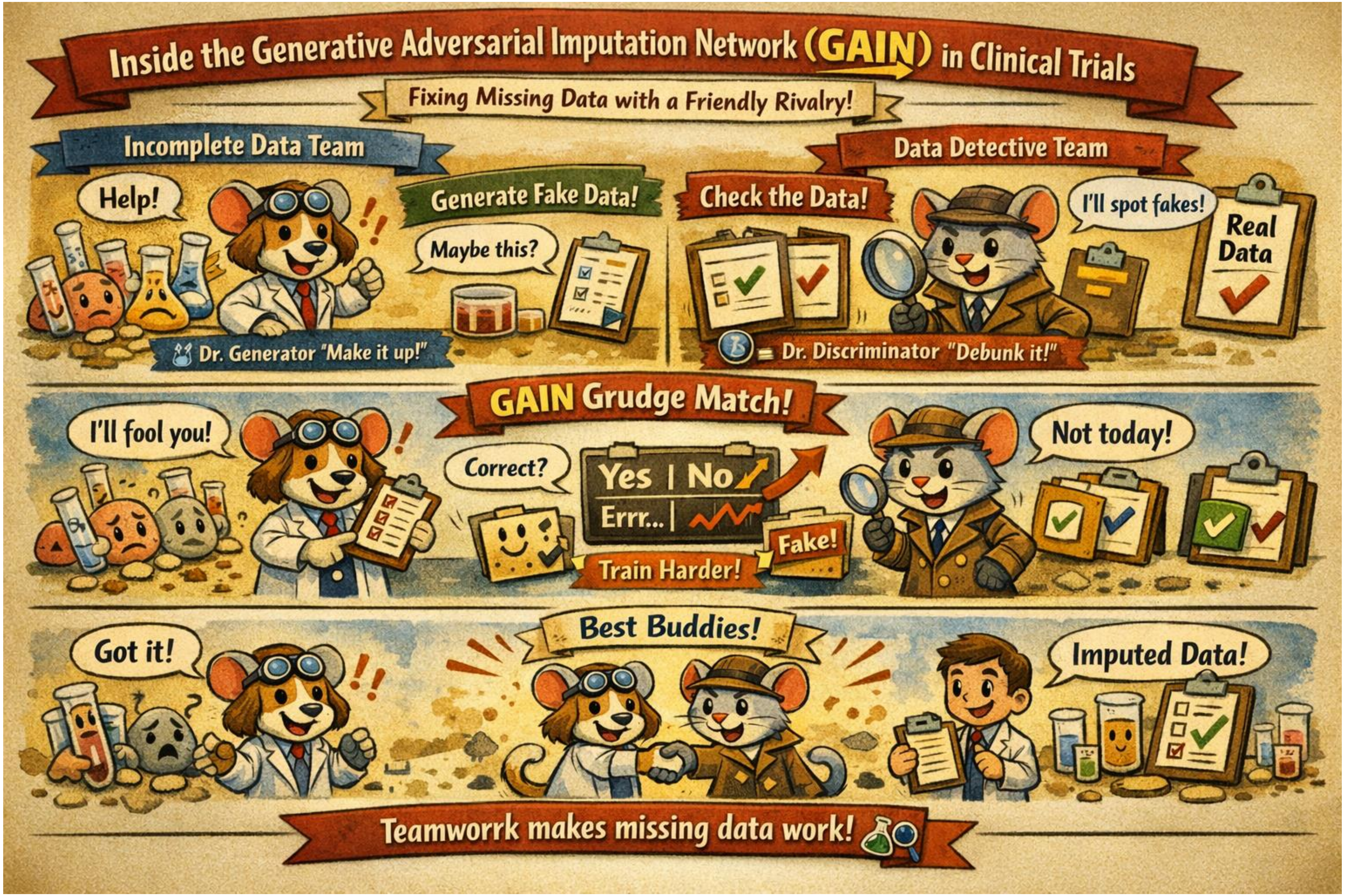
Converge

≤ 10 iterations until stable

3 Estimators – Bayesian Ridge, Random Forest, Predictive Mean Matching

Generative Adversarial Imputation Networks

1. Input
2. Mask Matrix
   (1 = observed & 0 = missing)
3. Initialize
   Fill missing values with random noise
4. Generator Network (G)
   Generates plausible values
5. Hint Mechanism
   Training & Stabilizes learning
6. Discriminator Network (D)
   Predicts value is observed or imputed
7. Adversarial Training
8. Converge



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Simulation

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Simulation1

Method	Variable	RMSE	MAE
MICE – Bayesian Ridge	HbA1c	$\boxed{0.2364}$	$\boxed{0.0637}$
MICE – Random Forest		0.2512	0.0686
MICE – PMM		0.3367	0.0937
GAIN		0.2707	0.0748

N = 1500 patients

Columns: Age, Sex, eGFR, LDL, Insulin, SBP, HbA1c phuse

Simulation2

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$$Y = 2A + 0.5W_1 + 0.7W_2 + \epsilon$$

Average Treatment Effect
(True ATE)

N = 1500 patients

W_1 = age (≈ 50±10), W_2 = severity, A = treatment (Drug A)

Y = outcome (disease improvement score)

ϵ = random noise

ATE

"If we switch our patient population from Drug B to Drug A, how much would the disease improvement score (Y) change on average?"

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Simulation2

MICE Approach

Imputation

↓

Regression

↓

Estimated ATE

GAIN + TMLE Approach

Imputation

↓

Regression

TMLE

↓

Prediction

↓

Targeting (Propensity Scores)

↓

Estimated ATE

Simulation2

Method	ATE	Difference (Estimated – True ATE) True ATE = 2	RMSE
Complete Case	1.56	-0.44	0.38
MICE	1.72	-0.28	0.15
GAIN + TMLE	2.18	$\boxed{0.18}$	$\boxed{0.07}$

Conclusion

MICE assumes the world is nice.
GAIN + TMLE prepares for when it isn't.

Not to replace MICE - but to explore what lies beyond when missingness tells a story.

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Thank You!

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