

PP10 Tipping Point Analysis in R and SAS: A Comparative Approach to Handling Missing Data in Clinical Research

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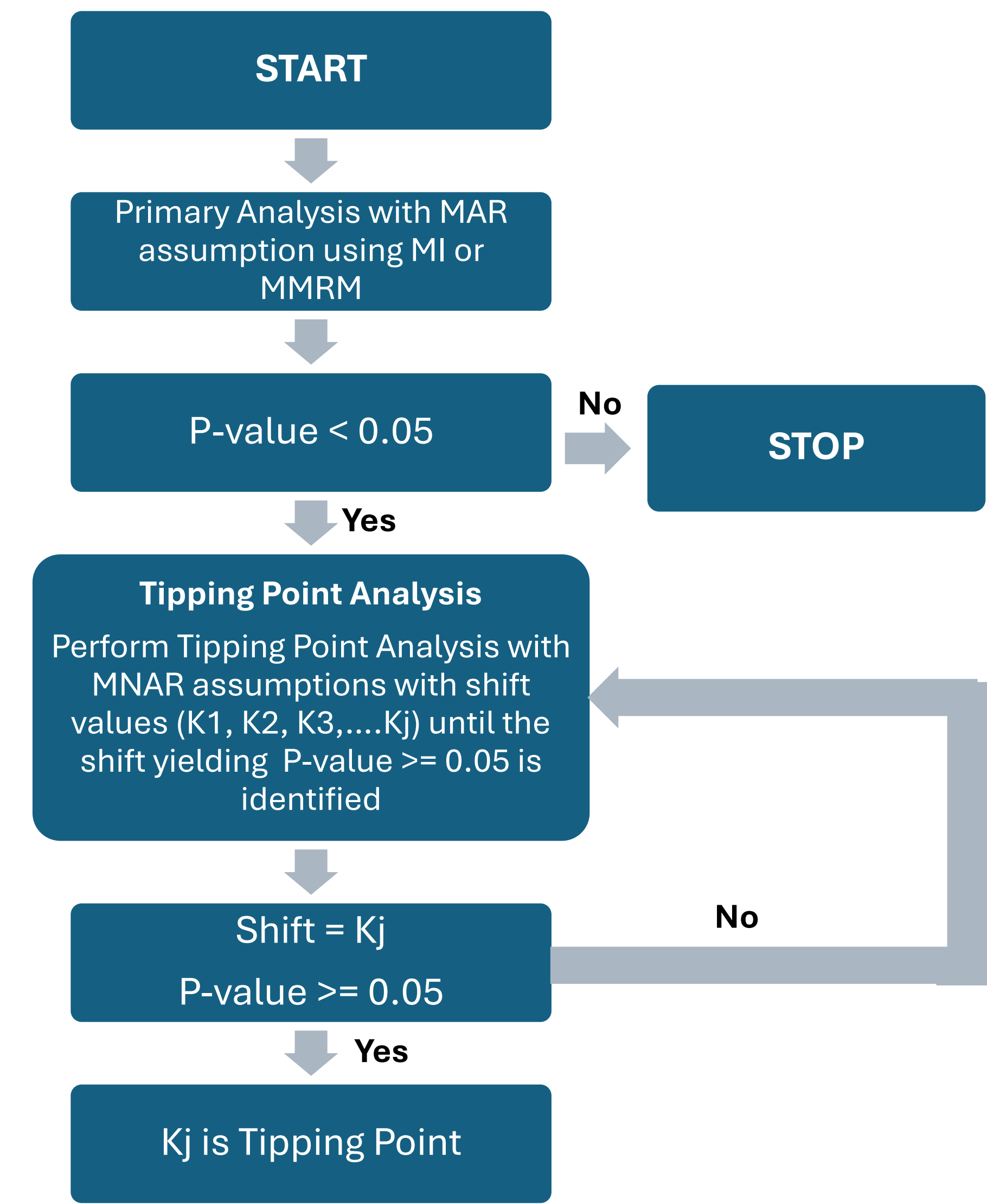
1. INTRODUCTION & BACKGROUND

What is Tipping Point Analysis (TPA)?

- Statistical technique to assess robustness of clinical trial results
- Evaluates impact of missing data on study conclusions
- Explores plausibility of missing data assumptions

When to Use TPA:

- ✓ Significant results in primary/secondary analyses
- ✓ Over 5% missing data
- ✓ Missing at Random (MAR) assumption made
- ✓ Regulatory requirement for Missing Not at Random (MNAR) sensitivity analysis



2. STUDY DESIGN

Simulated Clinical Trial Data

Objective: Assess antidepressant efficacy vs. placebo

Sample Size: 200 participants (100 per arm)

Outcome: Hamilton Depression Rating Scale (HAM-D)

Time Points: Baseline, Week 8, Week 16, Week 24

Missing Data: 26% (MAR assumption)

Treatment	Baseline Score	Age	Sex	Week 8 Score	Week 16 Score	Week 24 Score
Antidepressant	22	19	F	19	17	14
Antidepressant	24	29	M	22	21	18
Antidepressant	19	38	M	.	11	8
Antidepressant	22	18	M	15	12	11
Placebo	22	27	F	21	18	18
Placebo	20	38	F	16	.	17
Placebo	18	37	M	16	.	.

Example Data Structure

3. METHODOLOGY

Missing Data Patterns

Monotone: Sequential missing values

Arbitrary: Scattered missing values

Analysis Workflow:

Step 1: IMPUTATION

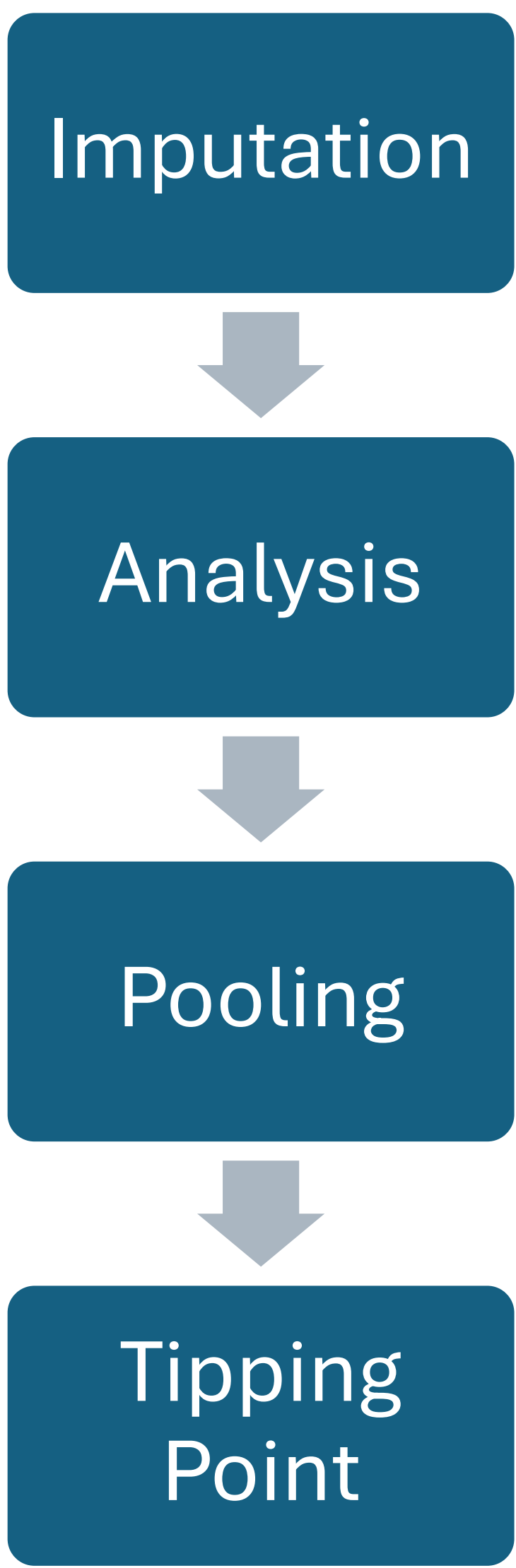
Convert arbitrary → monotone (MCMC method)
Impute remaining data (regression method)
Generate 25 imputed datasets

Step 2: PRIMARY ANALYSIS (MAR)

Fit ANCOVA model for each imputation
Pool results
Result: $p < 0.0001$ (significant)

Step 3: SENSITIVITY ANALYSIS (MNAR)

Apply incremental shifts ($K = 17-27$, identified through iterative exploration, then refined in increments of 1)
Re-analyze with shifted values
Identify tipping point ($p \geq 0.05$)



4. IMPLEMENTATION

SAS Approach:

- PROC MI (MCMC + Regression)
- PROC MIXED (Analysis)
- PROC MIANALYZE (Pooling)
- MNAR adjustment with shift parameter

R Approach:

- mice package (PMM method)
- lm() for ANCOVA
- Custom shift application
- Iterative p-value extraction

5. RESULTS

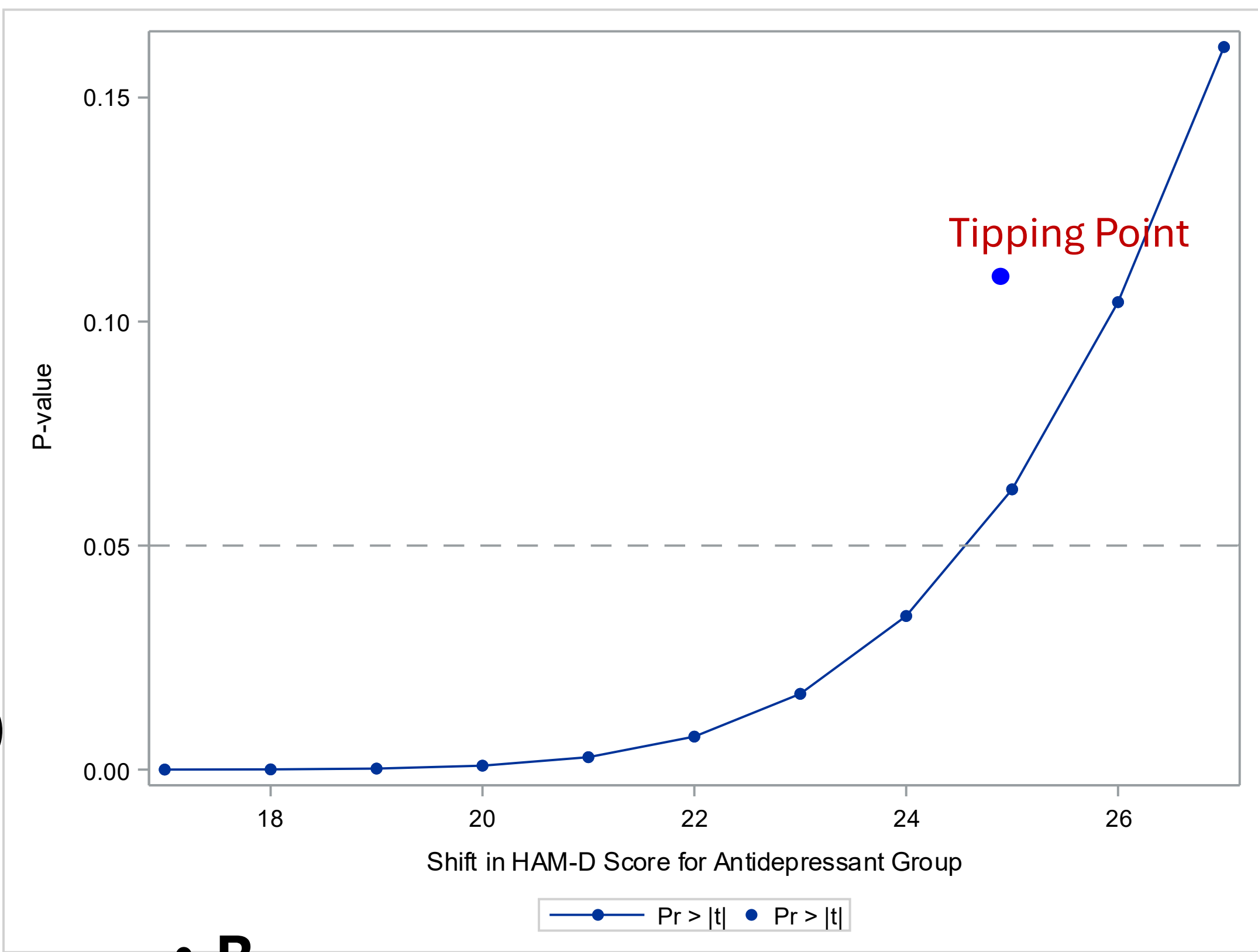
Primary Analysis (MAR)

$p < 0.0001$ ✓ Significant
Antidepressant effective in reducing depression

Tipping Point Analysis

• SAS

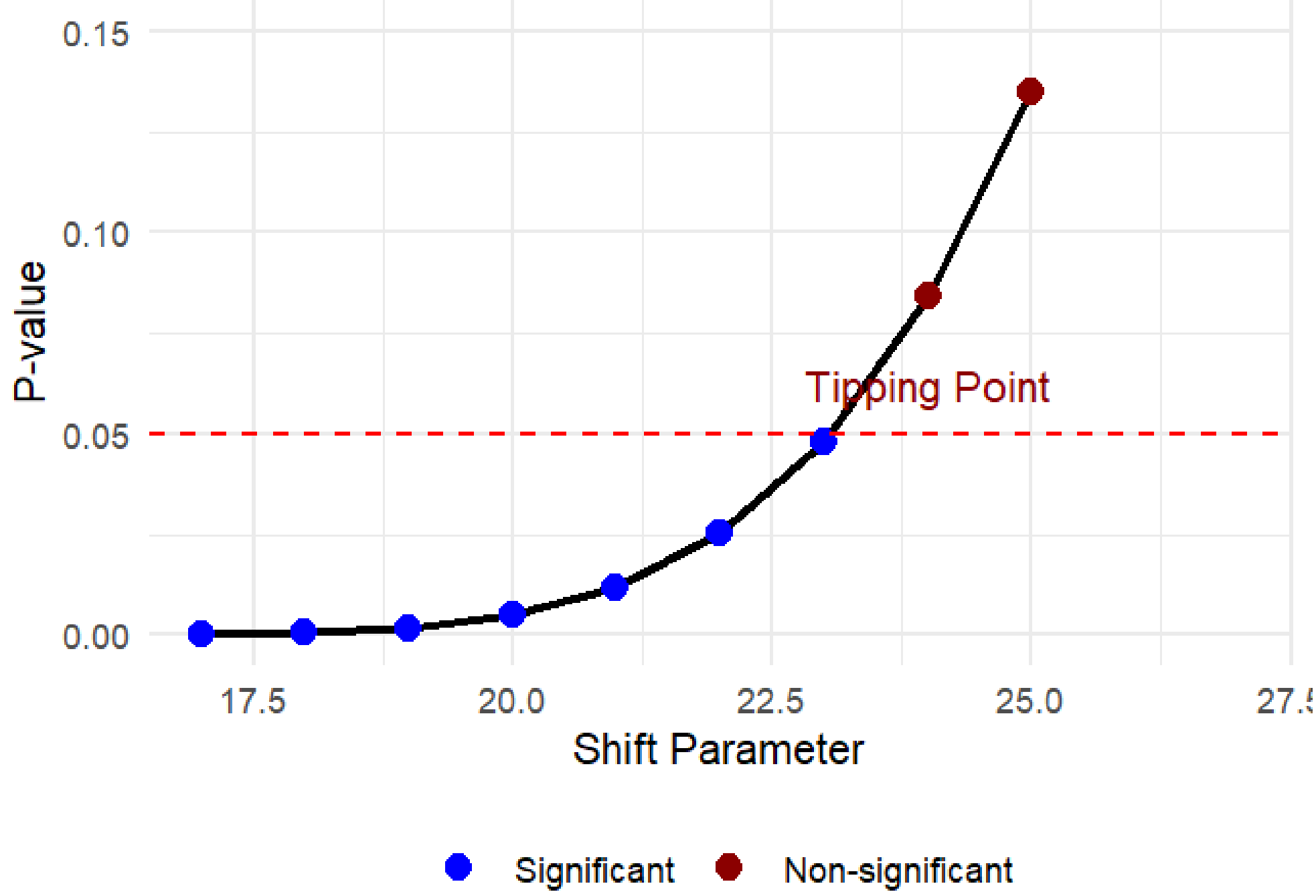
Treatment effect becomes non-significant at shift = 25



• R

Tipping Point Analysis

Treatment effect becomes non-significant at shift = 24



SAS Results:

Tipping point at **shift = 25**
Remains significant up to shift 24
p-value crosses 0.05 threshold at shift 25

R Results:

Tipping point at **shift = 24**
Remains significant up to shift 23
p-value crosses 0.05 threshold at shift 24

6. CONCLUSIONS

- ✓ **Tipping point range (24-25)** provides informative sensitivity boundary
- ✓ **Both platforms yield consistent conclusions** despite minor differences
- ✓ **Magnitude of shift required** suggests findings are robust to plausible MNAR mechanisms
- ✓ **Recommendation:** Use both platforms for critical analyses to validate findings
- ⚠ **Important:** Final interpretation should consider clinical judgment, not only statistical results

REFERENCES

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