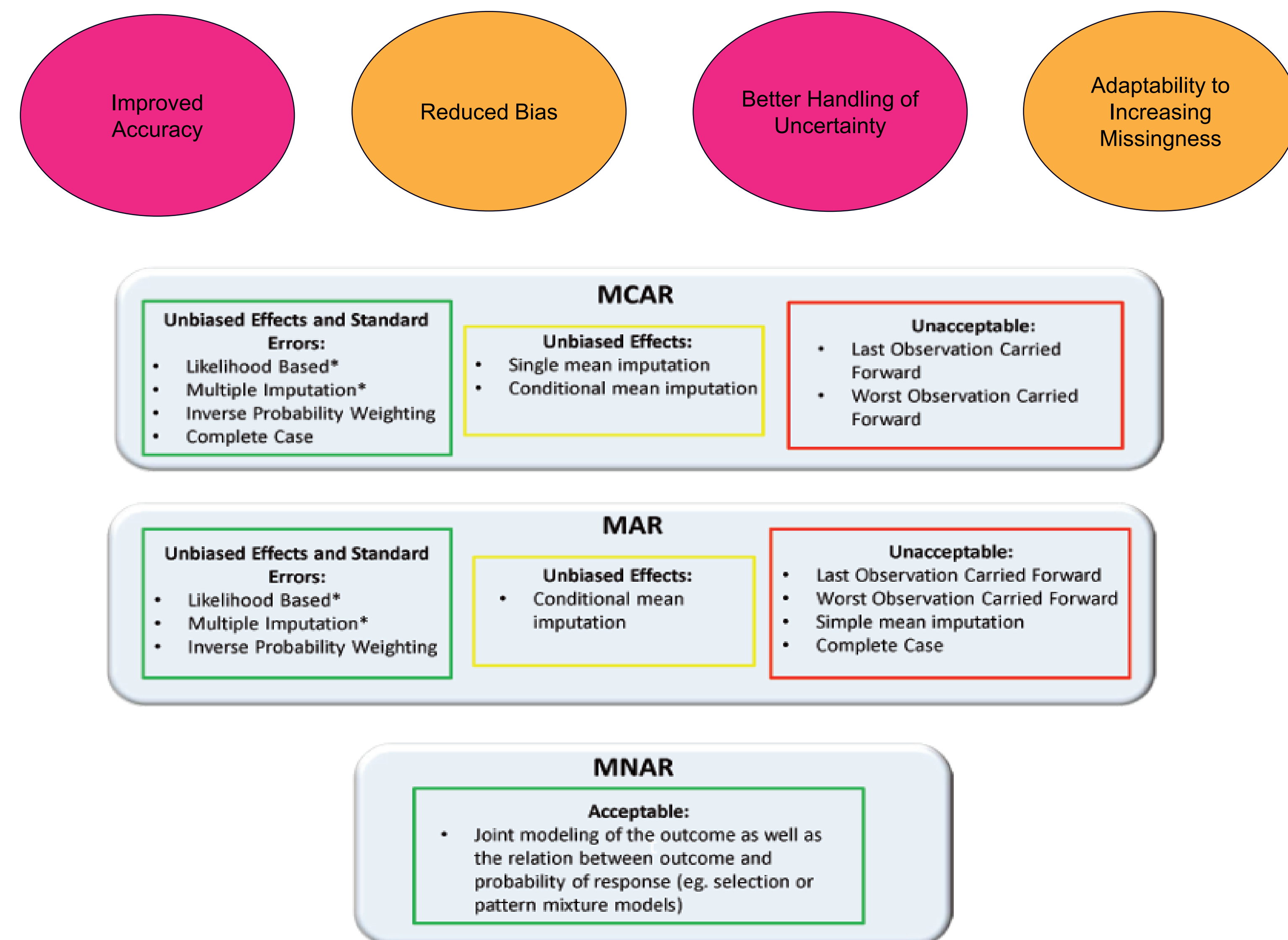


Introduction

Missing data are a common challenge in clinical research, with the potential to distort study findings by introducing bias and reducing statistical power if not managed correctly. Multiple imputation (MI) is a widely accepted method for addressing missing data.

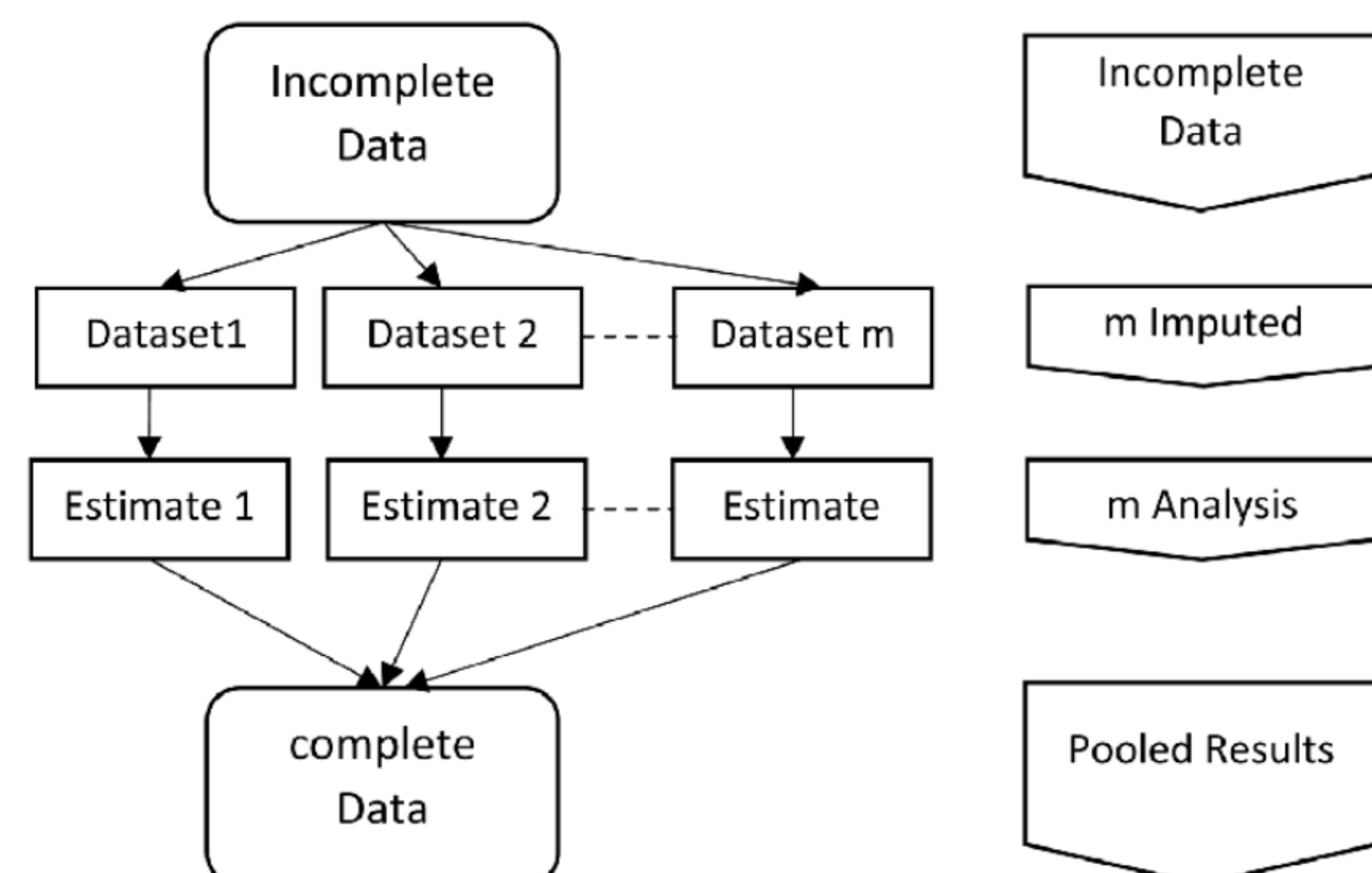
Despite the availability of advanced MI tools, evidence of their advantages over simpler approaches is mixed. Especially when the proportion of missingness is moderate and the data structure is relatively straightforward, simpler methods may perform just as well. The nature of the missingness is typically classified into three categories: Missing Completely at Random, Missing at Random, Missing Not at Random. Here, we aim to compare several MI approaches to a repeated measures framework applied to the same dataset.

Why Multiple Imputation?



*Preferred method as it uses all available data. Adopted from: Dziura et al.: Strategies for dealing with Missing data in clinical trials

Multiple Imputation Process



Study Design

Objective: Evaluate the effect of meds, administered as add-on to Anti-Condition meds regimen, in subjects with Cardiovascular condition

Subjects are randomized 1:1:1 to receive daily doses of Placebo, Arm 1 or Arm 2

Endpoint: Change in average Cardiovascular Measure from baseline at Month 12 in treatment arms

Primary analysis: ANCOVA using treatment, number of Anti-Condition Meds, their interaction, and baseline value

Methods and Results

In this study we had 16% of missingness at Month 12. We have run different methods on the data to handle the missingness. In all the approaches except approach 7, we are imputing the Month 12 value and none of the intermediate or covariate data are imputed.

Approach 1: Primary analysis was performed on 100 multiply imputed datasets using a Treatment Policy Approach, which takes account of on/off-treatment status using an interaction term, treatment-by-last on treatment visit.

Approach 2: Analysis was performed on 100 multiply imputed datasets using a Treatment Policy Approach, which imputes missing values using only the off-treatment retrieved dropouts based on their treatment arm.

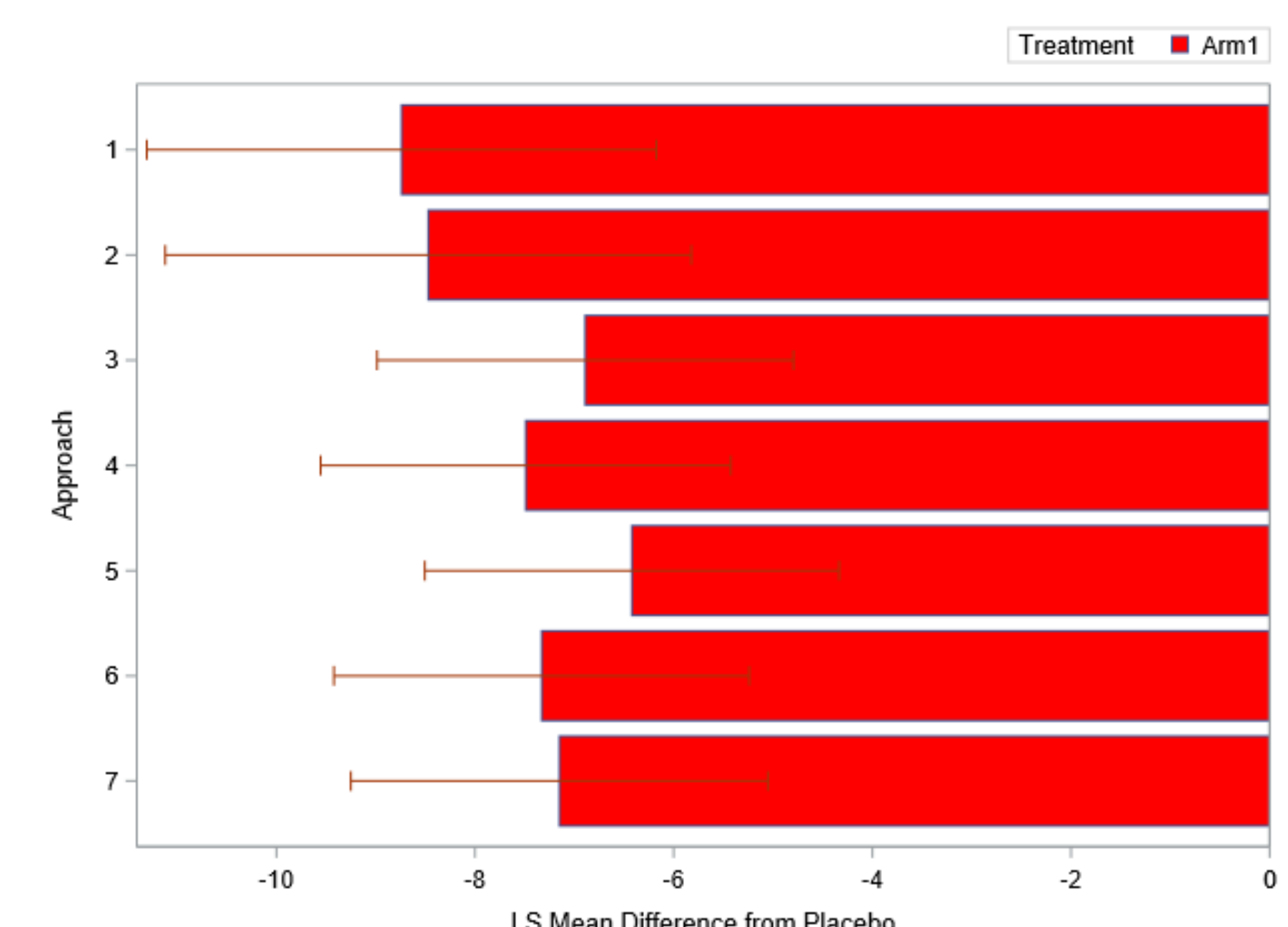
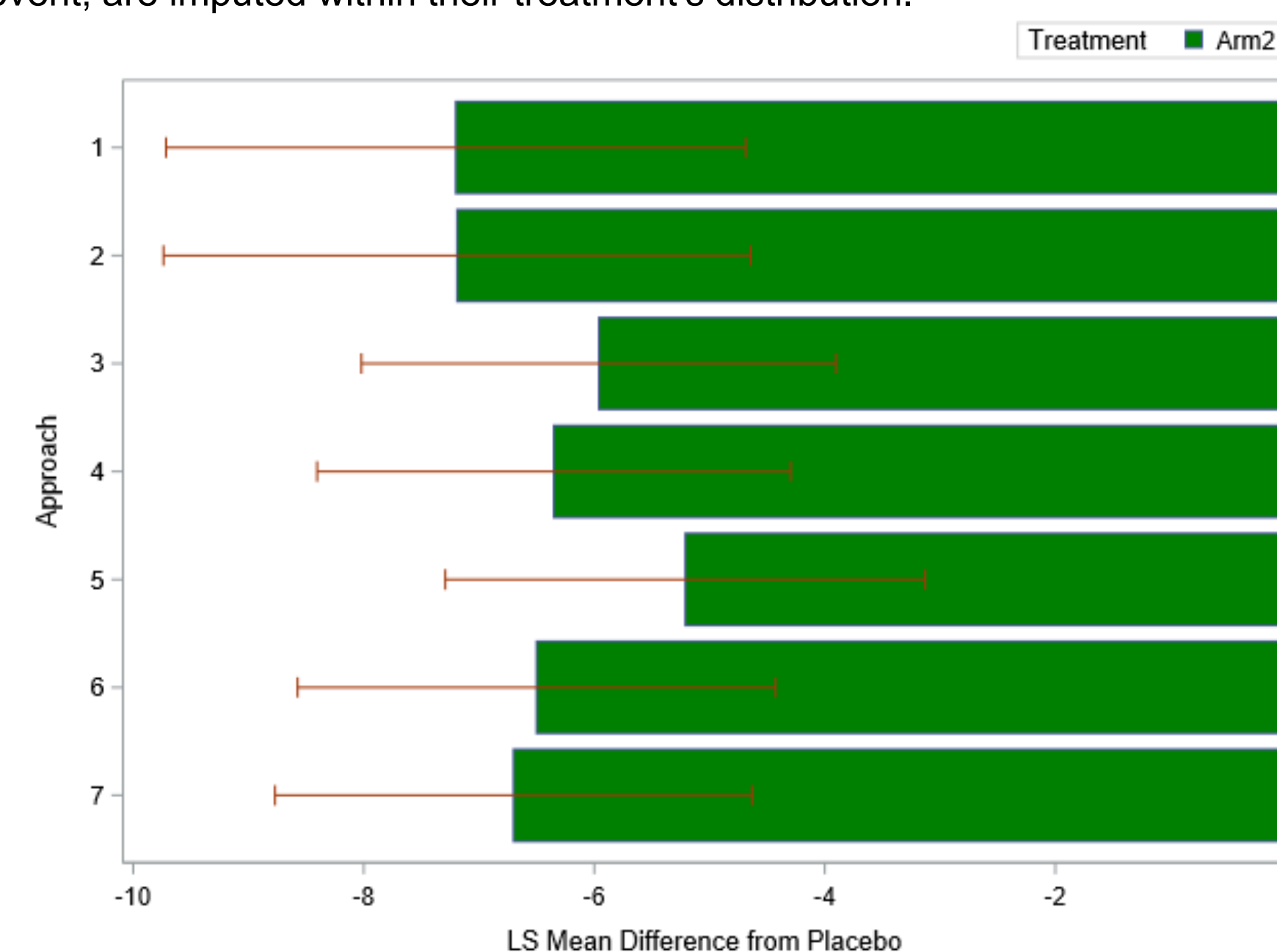
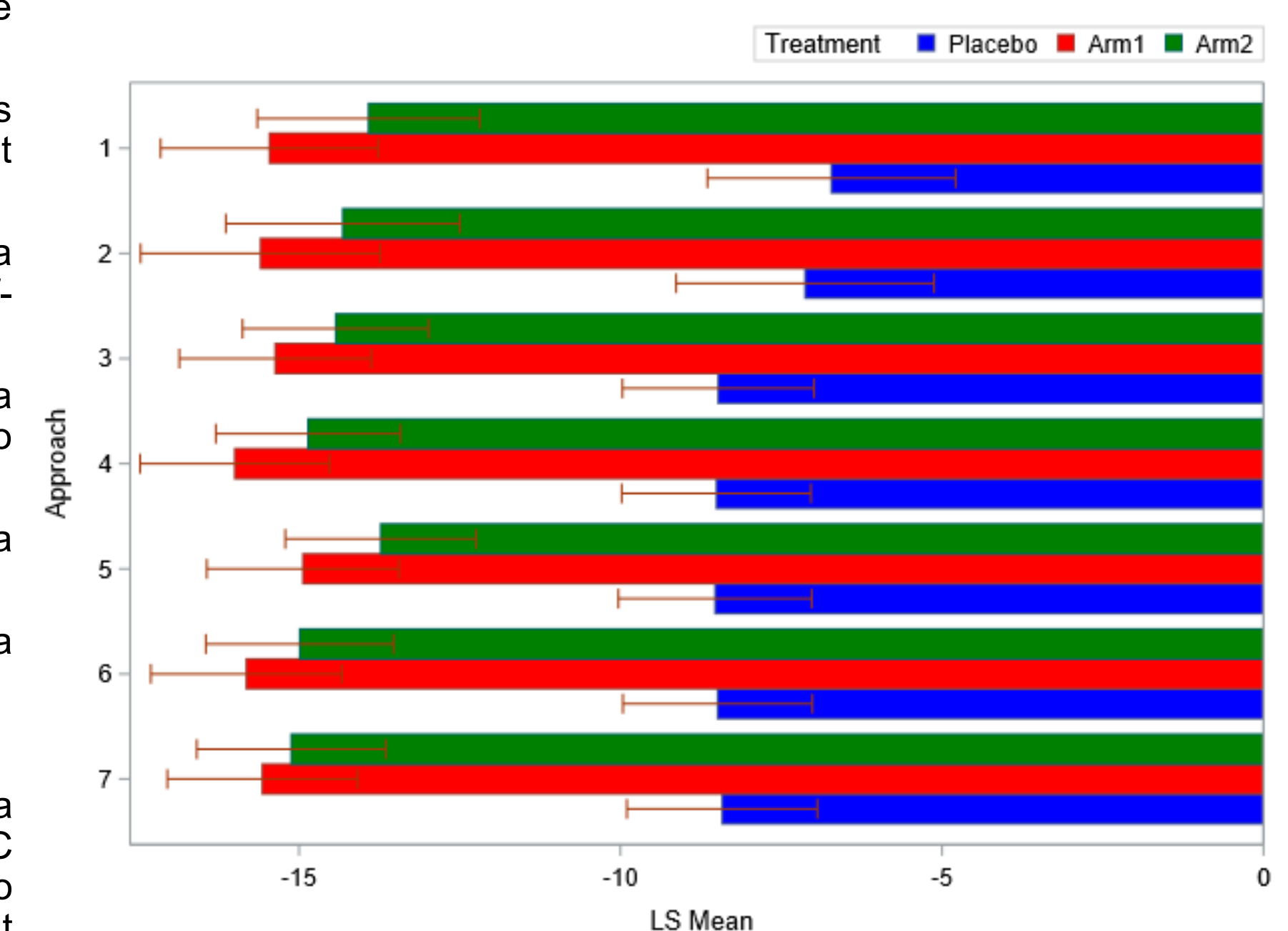
Approach 3: Analysis was performed on 100 multiply imputed datasets using a Reference Based Treatment Policy Approach. A reference-based approach to multiple imputation is implemented using the Five Macros set.

Approach 4: Analysis was performed on 100 multiply imputed datasets using a MAR approach.

Approach 5: Analysis was performed on 100 multiply imputed datasets using a NMAR approach.

Approach 6: No data are imputed for this ANCOVA. Observed data are used.

Approach 7: Analysis was performed on 100 multiply imputed datasets using a two-steps method. First intermediate missing data is imputed with MCMC approach. Patients with an intercurrent event are imputed using the Placebo distribution as a reference. Active Treatment patients without an intercurrent event, are imputed within their treatment's distribution.



Conclusions

Across the seven analytical approaches used to handle missing data, results were consistently aligned, underscoring the robustness of the treatment effect under a wide range of assumptions. Approaches 1–3, based on variations of the Treatment Policy framework, produced directionally similar estimates with no meaningful shifts in treatment effect. The MAR-based (Approach 4) and NMAR-based (Approach 5) sensitivity analyses likewise yielded results comparable to the primary analysis, indicating limited sensitivity to departures from the MAR assumption. Approach 6, an observed-case ANCOVA without imputation, also supported the primary findings despite relying on stronger assumptions about the missing-data mechanism. Approach 7 applied a two-step MI strategy across 100 imputed datasets: intermediate missing data were imputed using an MCMC procedure, patients with intercurrent events were imputed using the placebo distribution, and active-treatment patients without intercurrent events were imputed within their own treatment distribution. This method produced results consistent with the other approaches. This comparison helps assess whether more complex MI approaches offer meaningful advantages over simpler, more transparent alternatives. In this instance, the consistency of results across methods suggests that increasing methodological complexity does not materially change the substantive conclusions. This insight informs practical decision-making by indicating that straightforward MI strategies—or even observed-case analyses in some contexts—may be sufficient for routine analyses when the missing-data mechanism is not strongly informative.

All seven approaches produced similar results, suggesting that such a large set of methods may not always be necessary. Running multiple MI strategies adds time, computational burden, and requires extra justification to reviewers. A smaller, more focused set of approaches could offer the same insights with greater efficiency and clearer communication.