MSR48

# Using Bayesian Methodology to Minimize Control Recruitment in Trials of Relapsed and Refractory (RR) Multiple Myeloma (MM) Through Incorporation of Prior Control Response Information Borrowed From Real-World Evidence

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## Introduction

- Borrowing information from historical data to aid the estimation of a clinical trial has the **potential to reduce the required size of a control arm, while still maintaining power and inferential accuracy.**
- Minimizing control arm sizes is advantageous in oncology and rare diseases, where patient populations are small and enrollment into the control arm is often minimized for ethical reasons.
- **Bayesian methodology** provides a statistical framework which allows for the integration of historical evidence into a contemporary analysis.
- The application of **real-world data** (RWD) is increasingly being recognized as having the ability to improve the efficiency of regulatory approval. As most historical data borrowing analyses to date have focused on borrowing information from historical trials, **the viability of borrowing information from RWD requires assessment.**

## Objectives

1. **Build a cohort of RWD patients** with the necessary therapy history to be compared to the control arm of the **ICARIA-MM[1] cohort**.
2. **Construct PFS outcome data** using serology biomarkers and mortality data in the Arcturis-MM dataset.
3. **Investigate the similarity in progression-free survival (PFS)** between the constructed RWD cohort and the ICARIA-MM control arm.
4. Implement a Bayesian borrowing analysis where **information is borrowed from the RWD cohort** to estimate treatment effect for the ICARIA-MM cohort.

## Methods

1. Collection of MM data
- **Patients with MM (ICD-10 code C90.0)** were retrospectively identified between 2000 and 2023 from the Arcturis UK dataset using de-identified secondary care EHR.

2. Line of Therapy Construction
- **Arcturis' proprietary Lines of Therapy (LoT) algorithm** was applied to anti-cancer therapy data to construct patient lines of therapy.

3. Cohort identification:
- Patients (N = 110) receiving PomDex at 3L+ who had no prior daratumumab exposure, and who had prior proteasome inhibitor (PI) and lenalidomide exposure in the Arcturis-MM dataset were included in the RWD cohort. PFS was constructed using biomarker data in the Arcturis-MM dataset. Trial data (N = 307) for ICARIA-MM was extracted from published trial results[1].

4. Survival analysis:
- **Time-to-event analyses** used an exponential hazard model with PFS as the outcome and IsaPomDex exposure as a covariate.
- Survival modelling (trial analysis) of ICARIA-MM and the Arcturis-MM dataset RWD cohort (RWD analysis) was performed

5. Bayesian borrowing:
- Simulations were used to assess the impact of borrowing on the estimated treatment effect for ICARIA-MM. **Different randomization scenarios** spanning 1:2 (50% removed) to no concurrent controls (100% removed) were simulated by removing a sub-sample from the ICARIA-MM control arm.
- Borrowing (Figure 1) and no borrowing analyses were performed for each simulation.

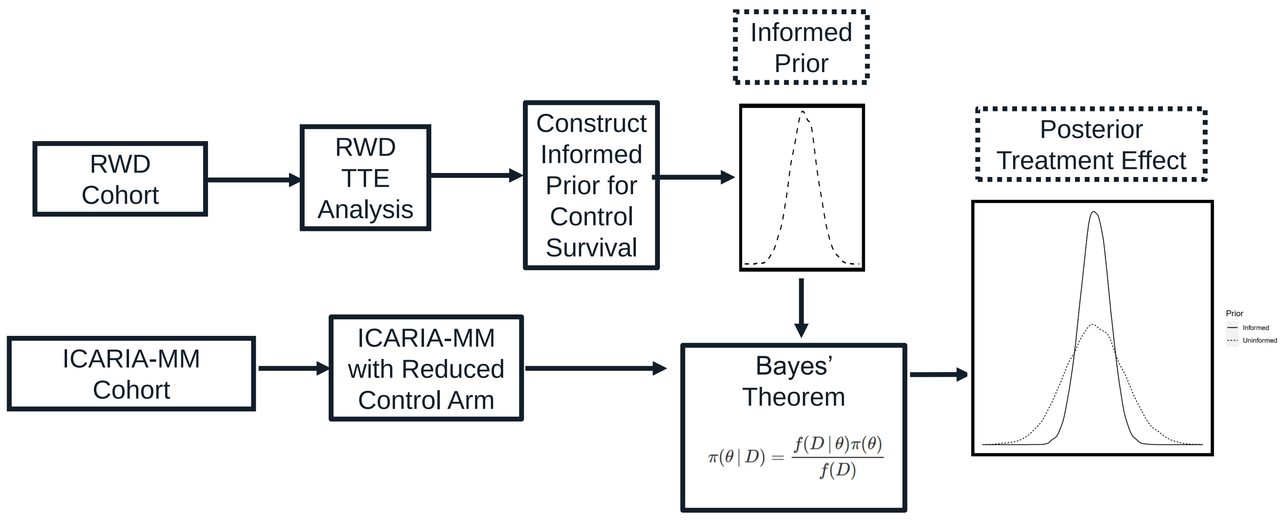


Figure 1: Schematic representation of the Bayesian borrowing process. A prior distribution for the baseline hazard is obtained from analysis of historical data. This prior is updated by ICARIA-MM trial data using Bayes' theorem to obtain a posterior estimate of the treatment effect, with a smaller variance than if no prior information was included

6. Comparison to trial data:
- The RWD analysis was used to construct an **informed prior for control survival** in all borrowing analyses. Posterior samples were obtained with JAGS[2]. The marginal posterior hazard ratio (HR) from each simulation and the HR from the trial analysis were compared for **bias, precision, and type 2 error**.

## Results

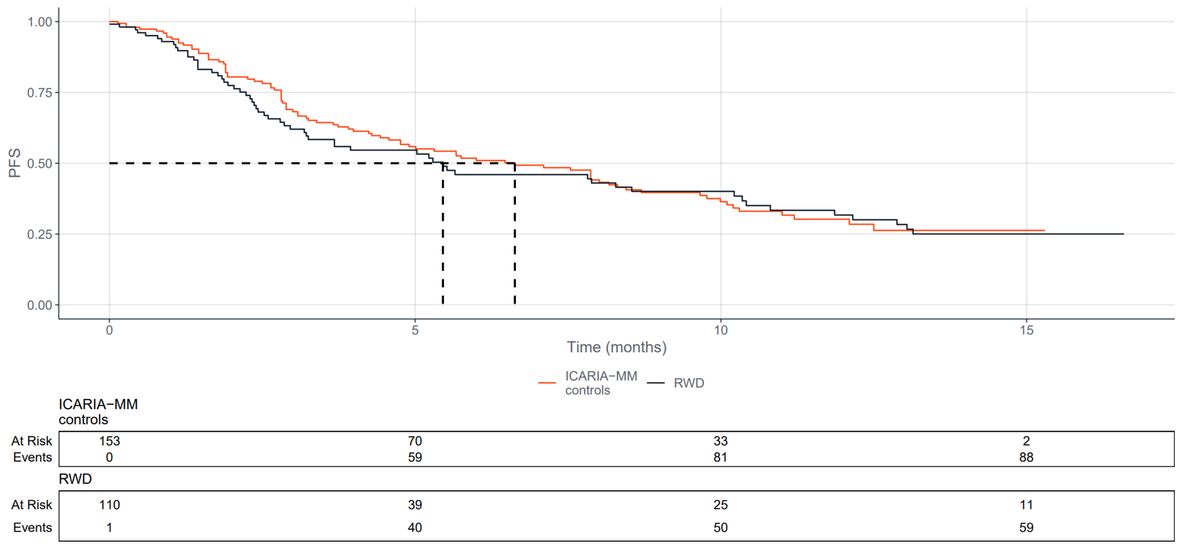


Figure 2: Kaplan-Meier curves comparing PFS between the **Arcturis-MM dataset** and the **ICARIA-MM control arm**. The dotted line represents the point of median survival in each cohort. The two survival distributions are generally comparable, with slight discrepancies around median survival and in the first 5 months of follow-up..

- PFS between both cohorts show **similar event time distributions**, with slight discrepancies around the median survival time (Figure 2)
- Reducing control arm enrolment in the absence of borrowing leads to an increase bias; **borrowing results in minimal bias** across all randomization scenarios (Figure 3 a)
- Posterior precision when borrowing is applied is **comparable** with precision obtained from the trial analysis (Figure 3 b)
- Reduction in control arm enrolment results in inflation of the type 2 error, but when borrowing is applied the **type 2 error rate equals zero across all scenarios** (Figure 3 c)

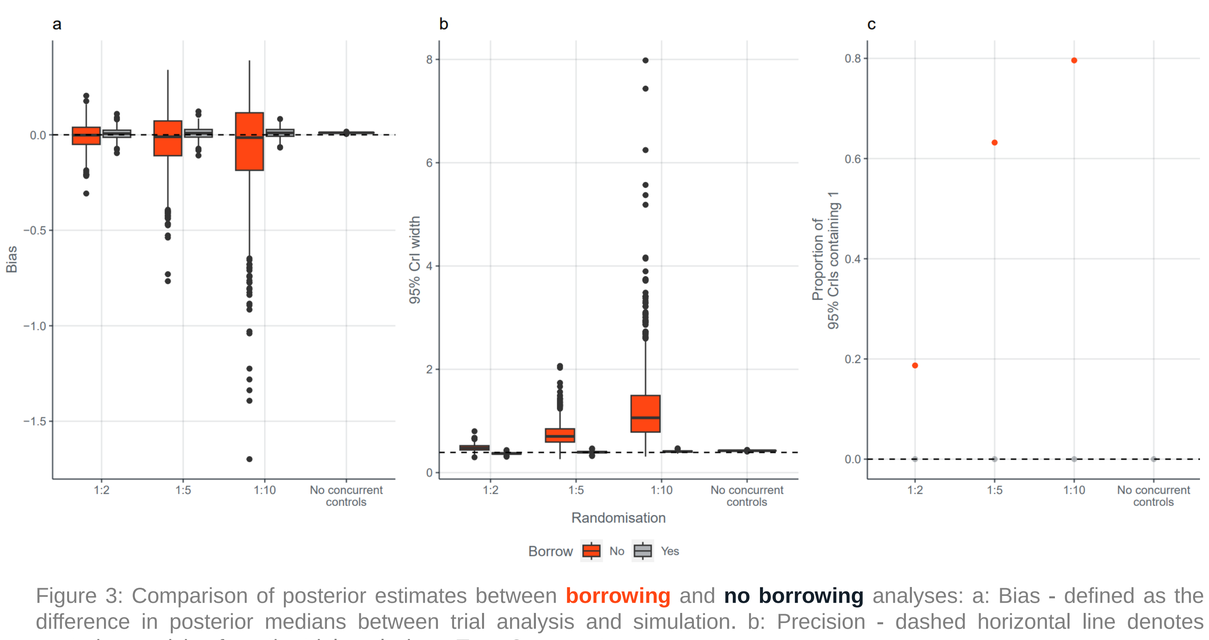


Figure 3: Comparison of posterior estimates between **borrowing** and **no borrowing** analyses: a: Bias - defined as the difference in posterior medians between trial analysis and simulation. b: Precision - dashed horizontal line denotes posterior precision from the trial analysis. c: Type-2 error rate

## Conclusions

- Bayesian borrowing from RWD **can reduce the control arm size while maintaining inferential accuracy.**
- Borrowing from RWD did not have a substantial impact on trial estimation, however a comparison of median PFS between RWD and ICARIA-MM control cohorts (Figure 2) suggested some discrepancy. Therefore, borrowing using a **refined RWD cohort** should be investigated.
- Further analyses investigating the benefits of **dynamic borrowing** methods, which **guard against any discrepancy in survival** between external and trial control data, are required.

## Acknowledgements

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## References

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[2] Plummer, M., 2003, March. JAGS: A program for analysis of Bayesian graphical models using Gibbs sampling. In *Proceedings of the 3rd international workshop on distributed statistical computing* (Vol. 124, No. 125.10, pp. 1-10)

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