Simulation Report

ROADMAP: RandOmised Arthroplasty infection worlDwide Multidomain Adaptive Platform trial - simulation report

Investigator initiated, Randomised Embedded Multifactorial Adaptive Platform (REMAP) trial, conducted across multiple hospitals in several regions of the world.

Version: 0.1

Date: 26 May 2025

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Sponsor:	University of Newcastle, NSW, Australia
Registration (ANZCTR):	todo
HREC	todo
Chief Investigator(s):	Professor Joshua Davis Professor Laurens Manning

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Study title:	ROADMAP: RandOmised Arthroplasty infection worlDwide Multidomain Adaptive Platform trial
Intervention:	Surgery type, backbone antibiotic duration, extended prophylaxis, antibiotic type
Study design:	Randomised Embedded Multifactorial Adaptive Platform trial
Sponsor:	University of Newcastle, NSW, Australia
Protocol:	Version 1.1 01AUG2024
Registration:	todo
HREC:	todo
Study date of first consent:	todo
Principal coordinating investigators:	Professor Joshua Davis and Professor Laurens Manning

Version history

Version	Date	Change	Reason
0.1	05/2025	First version	N/A

Repository status

```
## Local:    main /Users/mark/Documents/project/roadmap/src/roadmap-sap
## Remote:   main @ origin (https://github.com/maj-biostat/roadmap-sap.git)
## Head:     [fb39f77] 2025-05-26: First version
##
## Branches:         1
## Tags:             0
## Commits:         21
## Contributors:     1
## Stashes:          0
## Ignored files:    2
## Untracked files: 26
## Unstaged files:   2
## Staged files:     0
##
## Latest commits:
## [fb39f77] 2025-05-26: First version
## [4d28d41] 2025-05-26: Update decision section
## [af61397] 2025-05-26: Update subgroups
## [3b61110] 2025-05-22: Updates to estimand based on chat with jt
## [704d6e0] 2025-05-08: Latest rendered version
```

Preface

This simulation report documents the current set of reference simulations for ROADMAP. The simulation report is an operational document that will be updated, as necessary, over the course of the study. It should be read in conjunction with the relevant version of the statistical analysis plan (also contained in this respository).

1 Introduction

2 Data generation

Data is generated based on the empirical distributions obtained from the PIANO study, Browning et al. (2022) and domain experts.

We simulate silo membership from a multinomial distribution with probabilities 0.3, 0.5 and 0.2 for early, late and chronic. Conditional on silo membership, we simulate site of infection from a multinomial distribution with probabilities 0.4, 0.6 (knee, hip | early), 0.7, 0.3 (knee, hip | late) and 0.5, 0.5 (knee, hip | chronic).

For the surgical domain, we simulate preference towards revision from a multinomial distribution with probabilities 0.66, 0.33 (rev(1), rev(2) | early), 0.3, 0.7 (rev(1), rev(2) | late), 0.25, 0.75 (rev(1), rev(2) | chronic).

We simulate surgical intervention from a multinomial distribution with probabilities 0.85, 0.15 (DAIR, revision | early), 0.5, 0.5 (DAIR, revision | late), 0.2, 0.8 (DAIR, revision | chronic). Revision is subsequently decomposed into one and two-stage via the preferences.

A silo-specific index can be computed as where is the treatment allocation (DAIR, rev(1), rev(2)), is the number of surgical treatment types and is the silo membership (early, late, chronic).

For the antibiotic duration domain, we fix all participants that have received DAIR or two-stage revision as having non-randomised treatment. For all those receiving one-stage, we simulate antibiotic duration intervention from a multinomial distribution with probabilities 0.3, 0.35, 0.35 (non-rand, 12 weeks, 6 weeks | rev(1)). That is, 70% of the eligible set get randomised treatment and the split between 12 weeks and 6 weeks is 1:1.

For the extended prophylaxis domain, we fix all participants that have received DAIR or one-stage revision as having non-randomised treatment. For all those receiving one-stage, we simulate extended prophylaxis intervention from a multinomial distribution with probabilities 0.1, 0.45, 0.45 (non-rand, 12 weeks, 6 weeks | rev(2)). That is, 90% of the eligible set get randomised treatment and the split between 12 weeks and 6 weeks is 1:1.

For the antibiotic choice domain, we simulate the intervention from a multinomial distribution with probabilities 0.4, 0.3, 0.3 (non-rand, no-rifampicin, rifampicin) unconditional on silo membership. That is, 60% of the eligible set get randomised treatment and the split between no-rifampicin and rifampicin is 1:1.

As the trial progresses, decisions may be made which would lead to some allocations being shut off.

The true log-odds of response by subject is calculated as the sum of their parameters indexed by the levels generated above. Treatment success is simulated as a bernoulli random variable with probability equal to the inverse logit transform of the log-odds from the linear predictor. To speed up the model, we aggregate number of successes and number of trials by covariate group which gives the analogous binomial random variable representation.

3 Simulation model

We use a simplified version of the primary analysis model presented in the statistical analysis plan, section 2.6.

If, for whatever reason, the early or chronic silo show variation in the surgical domain effects adjustment for silo is inadequate to account for this and we end up with a polluted version of the surgical domain parameters. Most other things in the model remain the same as the previous simulation. The model is used to compute unit level risk (probability) and assesses decisions based on risk difference for the intervention comparisons by domain.

For the simulations, we have a single, multivariable logistic regression model with a linear predictor that incorporates all domains and is specified as follows:

$$
\begin{aligned}
Y &\sim \text{Binomial}(n, p) \\
\text{logit}(p) &= \mu + \beta_s + \beta_j + \beta_p + \\
&\quad \beta_{d1[k_{d1},s]} + \beta_{d2[k_{d2}]} + \beta_{d3[k_{d3}]} + \beta_{d4[k_{d4}]}
\end{aligned}
$$

for each distinct covariate grouping where:

- μ represents an overall reference level from which all covariates deviate
- β_s represents the silo deviations, which can be thought of as a seriousness of disease adjustment. We fix the first parameter (early) in this vector to zero for identifiability and the components are for early, late and chronic silo membership.
- β_j represents the joint deviations, accounting for heterogeneity in outcome due to site of infection. Again, we fix the first parameter (knee) in this vector to zero for identifiability and the components are knee and hip.
- β_p represents the (pre-revealed) preference adjustment, assuming revision was allocated but included irrespective of silo and what the assignment ultimately turned out to be. This accounts for heterogeneity in outcome due to clinical preference for revision type,

which can be thought of as expert elicitation on aspects of the patient state and clinical experience. Again, we fix the first parameter (preference one-stage revision) in this vector to zero for identifiability and the components are preference for one-stage or two-stage. Assuming revision is assigned, we would expect that the original preference would ultimately align with the type of revision received, but there is nothing enforcing this. Arguably, this could be restricted to the late-acute cohort, but we would need to extend the vector of parameters to accommodate for this. The preference indicators are also used to compute the sample weights for aggregating one and two-stage revision into a single overall revision effect.

- $\beta_{d1[k_{d1},s]}$ represents the silo-specific deviations associated with the surgery type. This accounts for heterogeneity in outcome due to surgery type and with the late-acute deviations taken as a randomised comparison of dair vs revision after the agreed weighting is applied. Again, we fix the first parameter (dair in the early cohort) in this vector to zero for identifiability and the components are dair, rev(1), rev(2) for each silo. The reason for the silo-specific context is that if revision effects exist in one silo but not another, then without this conditioning, we will end up with biased inference. For example, if (for whatever reason) there is an revision effect in the early domain but not the late-acute cohort then without this level of adjustment, we would end up reporting a revision effect when we shouldn't be; adjustment for silo doesn't protect us from this, even though it is perfectly collinear with a unit receiving non-randomised or randomised surgical treatment.
- $\beta_{d2[k_{d2}]}$ represents the deviations associated with backbone antibiotic duration. This accounts for heterogeneity in outcome due to the assigned backbone antibiotic duration. The first parameter (non-randomised treatment) in this vector is set to zero for identifiability and the components are non-randomised, 12 weeks and 6 weeks. The term is included in the model irrespective of what surgery type was received but only units receiving randomised and revealed one-stage are captured within the 12 week/6 week comparison. The other units contribute to the non-randomised set (which is essentially a nuissance variable that we don't particularly care about). We are assuming that there is no silo-specific (or any other) hetereogeneity for this comparison.
- $\beta_{d3[k_{d3}]}$ represents the deviations associated with extended prophylaxis duration. This accounts for heterogeneity in outcome due to the assigned extended prophylaxis duration. The first parameter (non-randomised treatment) in this vector is set to zero for identifiability and the components are non-randomised, no ext-proph and 12 weeks. The term is included in the model irrespective of what surgery type was received but only

units receiving randomised and revealed two-stage are captured within the none/12 week comparison. The other units contribute to the non-randomised set (which again is a nuissance variable that we don't particularly care about). We are assuming that there is no silo-specific hetereogeneity for this comparison.

- $\beta_{d4[k_{d4}]}$ represents the deviations associated with antibiotic choice. This accounts for heterogeneity in outcome due to the assigned antibiotic choice. The first parameter (non-randomised treatment) in this vector is set to zero for identifiability and the components are non-randomised, no rifampicin and rifampicin. The term is included for all units for which rifampicin may be indicated. The other units contribute to the non-randomised set. We are assuming that there is no silo-specific hetereogeneity for this comparison.

The simulation model isn't particularly complicated but the way that terms enter the model is convoluted and understanding the dependency implications and consequently interpretations is fairly challenging. For the actual trial analysis, the model will be revised to the equivalent Bernoulli likelihood on unit level data and also extended to account for site, randomisation period and prognostic covariates. Bar the surgical domain, for which 'by silo' deviations are implicit in the existing parameterisation, no further interactions are included. However, given that heterogeneity by site of infection (joint) is of interest (primarily in the surgical domain) the analysis plan will include specification to account for this (essentially by an additional set of surgical domain parameters for which each term could be partially pooled, if that aligns with the prior belief structure).

4 Decision procedures

5 Scenarios

6 Results

6.1 Probability of triggering decisions

6.2 Sample sizes

6.2.1 Enrolments

6.2.2 Information informing randomised comparisons

6.3 Parameter estimation

Proportion with treatment success

Browning, S., Manning, L., Metcalf, S., Paterson, D., Robinson, J., Clark, B., Davis, J., 2022. Characteristics and outcomes of culture-negative prosthetic joint infections from the prosthetic joint infection in australia and new zealand observational (PIANO) cohort study. Journal of Bone and Joint Infection 7, 203–211. https://doi.org/10.5194/jbji-7-203-2022