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.

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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
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Version history

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Repository status

```
## Local:    main /Users/mark/Documents/project/roadmap/src/roadmap-sap
## Remote:   main @ origin (https://github.com/maj-biostat/roadmap-sap.git)
## Head:     [7041484] 2025-06-19: Forgot to update to latest sim results
##
## Branches:         1
## Tags:             0
## Commits:         39
## Contributors:     1
## Stashes:          0
## Ignored files:    2
## Untracked files: 24
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## Staged files:     0
##
## Latest commits:
## [7041484] 2025-06-19: Forgot to update to latest sim results
## [4479125] 2025-06-19: Add release link
## [6c5a5ee] 2025-06-19: Update on branch usage
## [853bb61] 2025-06-19: Update reports
## [85f0e55] 2025-06-19: WIP
```

Preface

This simulation report documents the current set of simulations for the operating characteristics of the ROADMAP study. 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).

In this report, reference to the current statistical analysis report, means reference to SAP version 0.2.

1 Introduction

Data generation assumptions, modelling approaches, scenarios and results that were used to explore the ROADMAP design operating characteristics.

These results are based on simulation ID sim07-05 with 10000 trials run per scenario.

2 Data generation

Data is generated based on the empirical distributions obtained from the PIANO study, Browning et al. (2022) and domain experts. The data generated process is a simplification of reality but aims to capture the essential elements of the design. The distributional assumptions of each data component follows.

We simulate silo membership from a multinomial distribution with probabilities 0.3, 0.5 and 0.2 for early, late and chronic. Site of infection is not modelled as decisions are to be made on the overall pattern of response rather than joint specific estimates.

Each of the domain intervention allocations are simulated independently and then design rules are use to enforce the logical structure. We simulate both domain entry and allocation. All participants are assumed to enter into the surgical domain, albeit some receive non-randomised treatment.

For the surgical domain, we simulate clinical preference of revision type from a multinomial distribution with probabilities 0.65, 0.35 (rev(1), rev(2) | early), 0.3, 0.7 (rev(1), rev(2) | late), 0.25, 0.75 (rev(1), rev(2) | chronic). Surgical intervention allocations are simultated based on a binomial distribution with probabilities 0.15 (revision | early), 0.5 (revision | late), 0.8 (revision | chronic). The revision indicator is subsequently decomposed into one and two-stage based on the value of preferences.

For the antibiotic duration domain, we simulate entry from a binomial random variable with a probability of 0.7 across all silos and allocation to randomised treatment is 1:1 across all silos. For the extended prophylaxis domain, we simulate entry from a binomial random variable with a probability of 0.9 across all silos and allocation to randomised treatment is 1:1 across all silos. For the antibiotic choice domain, we simulate entry from a binomial random variable with a probability of 0.6 across all silos and allocation to randomised treatment is 1:1 across all silos.

Based on the unconditional entry and allocations, we overlay the design rules. For the surgical domain, allocation to the control state maps assignment to DAIR and allocation to revision maps to revision type based on preference.

For the antibiotic duration domain, if one-stage has been assigned as the revision type, then conditional on the entry indicator, the participant is assigned to non-randomised treatment or the allocation level.

For the extended prophylaxis domain, if two-stage has been assigned as the revision type, then conditional on the entry indicator, the participant is assigned to non-randomised treatment or the allocation level.

For the antibiotic choice domain, conditional on the entry indicator, the participant is assigned to non-randomised treatment or the allocation level.

The data is generated sequentially at the start of each interim analysis. As the trial progresses, decisions may be made which lead to some allocations being shut off and thus restricting the possible assignments.

The linear predictor is constructed conditional on the surgical domain intervention, see Section 3. 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 Modelling

In order to reduce computational burden, we use a simplified version of the primary analysis model presented in the statistical analysis plan, section 2.6. For the simulations, we have a single, multivariable logistic regression model with a linear predictor that incorporates all domains and is specified as follows:

$$
\begin{aligned}
Y &\sim \text{Binomial}(\pi, n) \\
\text{logit}(\pi) &= \alpha + \lambda_s + \delta \\
\delta &= \begin{cases} \beta_{1[d1,s]} + \beta_{4[d4]} + \phi_p & \text{(dair)} \\ \beta_{1[d1,s]} + \beta_{2[d2]} + \beta_{4[d4]} & \text{(one-stage)} \\ \beta_{1[d1,s]} + \beta_{3[d3]} + \beta_{4[d4]} + \phi_p & \text{(two-stage)} \end{cases}
\end{aligned}
$$

where Y is a binomial variable for the number of events out of n trials for a distinct covariate pattern occurring with probability π calculated from the linear predictor as follows:

- α reference level log-odds of a successful outcome
- λ_s silo membership s
- $\beta_{1[d_1,s]}$ surgical intervention d_1 in silo s
- $\beta_{2[d_2]}$ backbone antibiotic duration intervention d_2
- $\beta_{3[d_3]}$ extended prophylaxis duration intervention d_3
- $\beta_{4[d_4]}$ antibiotic choice intervention d_4
- ϕ_p surgeon preference for one/two stage, p, assuming unit randomised to revision

Relative to the primary analysis model, the simulation model is constructed with a binomial likelihood and excludes terms for time, region, site and prognostic variables. The manner in which terms enter the model is convoluted and understanding the dependency implications and consequently care is needed with the data preparation.

Bar the surgical domain, for which 'by silo' deviations are implicit in the existing parameterisation, no further interactions are included.

4 Decision procedures

Decision procedures follow those that are documented in the current SAP. In brief, at each interim, we assess the posterior and if a decision threshold is met, we make claims as directed by the results. Within the simulations, we assume the decisions are binding and constrain the subsequent data generation options. Specifically, if a superiority decision is reached in one of the domains for which this decision type is relevant, then we consider that domain complete and all subsequent participants are assigned to receive the superior intervention. Non-inferiority is handled in an analogous manner. If a futility decision is reached (either for superiority of non-inferiority, as applicable for the given domain) then we consider that domain completed and all subsequent participants are assigned to receive the reference intervention.

In all cases, we continue to update the full joint posterior until we get to the point where all questions have been answered across all domains, at which point the trial will stop.

5 Scenarios

Each scenario adopted a maximum sample size of 2500 with interim analyses run after each 500 participants reach the primary endpoint. For simplicity, the treatment effects were specified on the log odds scale with treatment effects calibrated to target the domain level treatment effects in terms of risk differences. All scenarios used the same reference values and decision thresholds. After a long period of iteration, Table 5.1 shows the current set of simulation scenarios considered as the reference set for the design.

Table 5.1: ROADMAP simulation scenarios

ID	Scenario
1	RD = 0 in all domains +silo specific d1
2	RD = 0.12: surgical revision (one and two-stage) +silo specific d1
3	RD = 0.12: surgical revision (one-stage only) +silo specific d1
4	RD = 0.12: surgical revision (two-stage only) +silo specific d1
5	RD = 0.12: abx duration 6wk effect +silo specific d1
6	RD = 0.12: ext-proph 12wk effect +silo specific d1
7	RD = 0.12: abx choice rif effect +silo specific d1
8	RD = 0.12: all domains +silo specific d1
9	RD = -0.05: abx duration 6wk effect +silo specific d1
10	RD = 0.12 surgical, RD = 0.08 abx choice +silo specific d1

6 Results

6.1 Probability of triggering decisions

Table 6.1 provides the cumulative probability of decision types by domain. For the Surgical, Extended prophylaxis and Choice domains, the results indicate the cumulative probability of a superiority decision with the probability of futility for the superiority decisions in parentheses. For the Antibiotic duration domain, the results indicate the cumulative probability of a non-inferiority decision with the probability of futility for the non-inferiority decisions in parentheses.

Table 6.1: Cumulative probability of decision at each interim (enrolment by interim)

		Cumulative probability of decision as applicable to domain				
Domain	Decision type	500	1000	1500	2000	2500
RD = 0 in all domains +silo specific d1						
Surgical	Superiority (fut)	0.021 (0.538)	0.037 (0.709)	0.051 (0.79)	0.06 (0.839)	0.066 (0.869)
AB Duration	NI (fut)	0.112 (0.088)	0.181 (0.131)	0.231 (0.164)	0.275 (0.185)	0.309 (0.203)
AB Ext-proph	Superiority (fut)	0.04 (0.543)	0.062 (0.685)	0.076 (0.755)	0.085 (0.797)	0.092 (0.824)
AB Choice	Superiority (fut)	0.01 (0.653)	0.016 (0.83)	0.021 (0.905)	0.024 (0.94)	0.027 (0.96)
RD = 0.12: surgical revision (one and two-stage) +silo specific d1						
Surgical	Superiority (fut)	0.318 (0.068)	0.557 (0.091)	0.703 (0.099)	0.795 (0.104)	0.842 (0.105)
AB Duration	NI (fut)	0.115 (0.088)	0.203 (0.145)	0.274 (0.183)	0.336 (0.212)	0.387 (0.231)
AB Ext-proph	Superiority (fut)	0.042 (0.545)	0.067 (0.727)	0.085 (0.818)	0.095 (0.858)	0.1 (0.881)
AB Choice	Superiority (fut)	0.009 (0.661)	0.014 (0.837)	0.02 (0.911)	0.024 (0.946)	0.025 (0.963)
RD = 0.12: surgical revision (one-stage only) +silo specific d1						
Surgical	Superiority (fut)	0.043 (0.393)	0.085 (0.539)	0.117 (0.618)	0.144 (0.671)	0.167 (0.707)
AB Duration	NI (fut)	0.11 (0.092)	0.186 (0.14)	0.243 (0.173)	0.284 (0.194)	0.32 (0.212)
AB Ext-proph	Superiority (fut)	0.037 (0.542)	0.059 (0.69)	0.074 (0.764)	0.086 (0.809)	0.092 (0.837)
AB Choice	Superiority (fut)	0.011 (0.647)	0.019 (0.825)	0.024 (0.901)	0.028 (0.94)	0.03 (0.957)

Table 6.1: Cumulative probability of decision at each interim (enrolment by interim)

		Cumulative probability of decision as applicable to domain				
Domain	Decision type	500	1000	1500	2000	2500
RD = 0.12: surgical revision (two-stage only) +silo specific d1						
Surgical	Superiority (fut)	0.201 (0.132)	0.379 (0.177)	0.509 (0.202)	0.602 (0.215)	0.664 (0.223)
AB Duration	NI (fut)	0.104 (0.093)	0.185 (0.141)	0.247 (0.177)	0.305 (0.203)	0.353 (0.222)
AB Ext-proph	Superiority (fut)	0.038 (0.545)	0.063 (0.722)	0.079 (0.808)	0.087 (0.854)	0.093 (0.88)
AB Choice	Superiority (fut)	0.01 (0.654)	0.018 (0.832)	0.022 (0.904)	0.026 (0.941)	0.028 (0.959)
RD = 0.12: abx duration 6wk effect +silo specific d1						
Surgical	Superiority (fut)	0.021 (0.518)	0.036 (0.691)	0.049 (0.777)	0.06 (0.827)	0.066 (0.861)
AB Duration	NI (fut)	0.38 (0.012)	0.595 (0.016)	0.717 (0.017)	0.796 (0.018)	0.853 (0.018)
AB Ext-proph	Superiority (fut)	0.038 (0.55)	0.061 (0.692)	0.073 (0.764)	0.082 (0.807)	0.087 (0.835)
AB Choice	Superiority (fut)	0.008 (0.654)	0.016 (0.829)	0.021 (0.906)	0.025 (0.941)	0.027 (0.958)
RD = 0.12: ext-proph 12wk effect +silo specific d1						
Surgical	Superiority (fut)	0.028 (0.486)	0.047 (0.66)	0.061 (0.748)	0.073 (0.801)	0.08 (0.837)
AB Duration	NI (fut)	0.113 (0.087)	0.193 (0.132)	0.241 (0.162)	0.282 (0.184)	0.315 (0.202)
AB Ext-proph	Superiority (fut)	0.385 (0.088)	0.607 (0.106)	0.72 (0.113)	0.785 (0.118)	0.822 (0.119)
AB Choice	Superiority (fut)	0.009 (0.664)	0.017 (0.831)	0.022 (0.905)	0.026 (0.942)	0.029 (0.958)
RD = 0.12: abx choice rif effect +silo specific d1						
Surgical	Superiority (fut)	0.019 (0.538)	0.035 (0.71)	0.045 (0.795)	0.055 (0.842)	0.062 (0.871)
AB Duration	NI (fut)	0.107 (0.09)	0.176 (0.138)	0.227 (0.17)	0.268 (0.193)	0.305 (0.21)
AB Ext-proph	Superiority (fut)	0.042 (0.545)	0.062 (0.688)	0.075 (0.758)	0.083 (0.805)	0.09 (0.831)
AB Choice	Superiority (fut)	0.458 (0.037)	0.802 (0.04)	0.925 (0.041)	0.954 (0.042)	0.96 (0.042)
RD = 0.12: all domains +silo specific d1						
Surgical	Superiority (fut)	0.38 (0.046)	0.618 (0.063)	0.753 (0.07)	0.828 (0.074)	0.872 (0.077)
AB Duration	NI (fut)	0.417 (0.007)	0.728 (0.009)	0.878 (0.009)	0.946 (0.01)	0.97 (0.01)
AB Ext-proph	Superiority (fut)	0.434 (0.074)	0.74 (0.089)	0.861 (0.093)	0.896 (0.094)	0.907 (0.094)
AB Choice	Superiority (fut)	0.473 (0.035)	0.815 (0.04)	0.924 (0.041)	0.953 (0.041)	0.96 (0.041)
RD = -0.05: abx duration 6wk effect +silo specific d1						
Surgical	Superiority (fut)	0.019 (0.533)	0.036 (0.695)	0.048 (0.778)	0.059 (0.826)	0.066 (0.859)
AB Duration	NI (fut)	0.058 (0.166)	0.09 (0.26)	0.109 (0.324)	0.124 (0.374)	0.135 (0.414)
AB Ext-proph	Superiority (fut)	0.035 (0.547)	0.057 (0.684)	0.069 (0.755)	0.078 (0.801)	0.085 (0.832)
AB Choice	Superiority (fut)	0.011 (0.651)	0.016 (0.835)	0.019 (0.91)	0.023 (0.944)	0.025 (0.961)
RD = 0.12 surgical, RD = 0.08 abx choice +silo specific d1						
Surgical	Superiority (fut)	0.322 (0.07)	0.566 (0.091)	0.709 (0.101)	0.792 (0.107)	0.842 (0.11)

Table 6.1: Cumulative probability of decision at each interim (enrolment by interim)

		Cumulative probability of decision as applicable to domain				
Domain	Decision type	500	1000	1500	2000	2500
AB Duration	NI (fut)	0.114 (0.091)	0.206 (0.142)	0.281 (0.179)	0.344 (0.204)	0.4 (0.223)
AB Ext-proph	Superiority (fut)	0.038 (0.56)	0.062 (0.743)	0.077 (0.832)	0.086 (0.873)	0.091 (0.895)
AB Choice	Superiority (fut)	0.482 (0.032)	0.828 (0.035)	0.936 (0.035)	0.963 (0.036)	0.968 (0.036)

6.2 Sample size

6.2.1 Expected sample size for randomised comparisons

Table 6.2 and Figure 6.1 show the expected sample size by interim analysis for the randomised comparisons in each domain. When domain level decisions are triggered, subsequent enrolments are redirected to the remaining arms, which leads to the observed divergence between arms. The figures are to give a sense of how much information is available for estimating quantities that lead to trial decisions.

Table 6.2: Expected number of participants entering into randomised comparisons

		Expected sample size for randomised comparisons by enrolment				
Domain	Treatment arm	500	1000	1500	2000	2500
RD = 0 in all domains +silo specific d1						
Surgical	DAIR	125	305	480	640	784
Surgical	rev(1)	37	55	67	76	82
Surgical	rev(2)	88	129	157	177	191
Surgical	Revision	125	185	224	252	273
AB Duration	12 weeks	25	43	57	68	78
AB Duration	6 weeks	25	44	59	71	82
AB Ext-proph	6 weeks	70	141	203	256	301
AB Ext-proph	12 weeks	70	95	110	121	130
AB Choice	No-rif	150	384	614	825	1,012
AB Choice	Rif	150	203	231	246	257
RD = 0.12: surgical revision (one and two-stage) +silo specific d1						
Surgical	DAIR	125	217	280	321	350
Surgical	rev(1)	37	82	127	166	198

Table 6.2: Expected number of participants entering into randomised comparisons

		Expected sample size for randomised comparisons by enrolment				
Domain	Treatment arm	500	1000	1500	2000	2500
Surgical	rev(2)	87	192	296	387	462
Surgical	Revision	125	274	423	553	660
AB Duration	12 weeks	25	52	77	98	115
AB Duration	6 weeks	25	53	80	103	121
AB Ext-proph	6 weeks	70	184	302	407	494
AB Ext-proph	12 weeks	70	109	136	155	169
AB Choice	No-rif	150	388	615	807	961
AB Choice	Rif	150	202	228	242	250
RD = 0.12: surgical revision (one-stage only) +silo specific d1						
Surgical	DAIR	125	286	442	584	711
Surgical	rev(1)	38	62	80	96	108
Surgical	rev(2)	87	144	188	223	252
Surgical	Revision	125	205	268	318	360
AB Duration	12 weeks	25	45	62	76	87
AB Duration	6 weeks	25	46	63	79	92
AB Ext-proph	6 weeks	70	152	227	293	350
AB Ext-proph	12 weeks	70	98	115	128	138
AB Choice	No-rif	150	385	620	834	1,025
AB Choice	Rif	150	204	232	249	260
RD = 0.12: surgical revision (two-stage only) +silo specific d1						
Surgical	DAIR	125	239	330	403	459
Surgical	rev(1)	38	77	115	150	180
Surgical	rev(2)	88	179	269	350	419
Surgical	Revision	125	255	384	500	599
AB Duration	12 weeks	25	50	74	94	112
AB Duration	6 weeks	25	51	76	98	117
AB Ext-proph	6 weeks	70	176	287	388	477
AB Ext-proph	12 weeks	70	105	130	147	160
AB Choice	No-rif	150	390	627	836	1,014
AB Choice	Rif	150	203	230	247	257
RD = 0.12: abx duration 6wk effect +silo specific d1						
Surgical	DAIR	125	293	437	548	631
Surgical	rev(1)	37	56	68	75	80
Surgical	rev(2)	88	131	159	176	188
Surgical	Revision	125	187	226	252	268

Table 6.2: Expected number of participants entering into randomised comparisons

		Expected sample size for randomised comparisons by enrolment				
Domain	Treatment arm	500	1000	1500	2000	2500
AB Duration	12 weeks	25	37	43	48	50
AB Duration	6 weeks	25	49	68	83	93
AB Ext-proph	6 weeks	70	141	196	236	265
AB Ext-proph	12 weeks	70	94	109	118	124
AB Choice	No-rif	150	373	567	717	827
AB Choice	Rif	150	203	229	243	251
RD = 0.12: ext-proph 12wk effect +silo specific d1						
Surgical	DAIR	125	299	469	624	763
Surgical	rev(1)	38	58	71	81	89
Surgical	rev(2)	88	134	166	189	207
Surgical	Revision	125	192	238	271	296
AB Duration	12 weeks	25	44	58	70	80
AB Duration	6 weeks	25	44	60	74	85
AB Ext-proph	6 weeks	70	106	126	139	148
AB Ext-proph	12 weeks	70	135	196	250	297
AB Choice	No-rif	150	387	619	830	1,017
AB Choice	Rif	150	202	229	244	253
RD = 0.12: abx choice rif effect +silo specific d1						
Surgical	DAIR	125	307	484	641	782
Surgical	rev(1)	38	56	67	75	81
Surgical	rev(2)	87	130	157	176	190
Surgical	Revision	125	185	224	251	271
AB Duration	12 weeks	25	43	57	69	78
AB Duration	6 weeks	25	44	58	71	81
AB Ext-proph	6 weeks	70	143	205	256	300
AB Ext-proph	12 weeks	70	94	109	120	128
AB Choice	No-rif	150	236	270	283	291
AB Choice	Rif	150	355	579	788	972
RD = 0.12: all domains +silo specific d1						
Surgical	DAIR	125	207	256	285	301
Surgical	rev(1)	38	85	117	133	140
Surgical	rev(2)	88	198	274	311	327
Surgical	Revision	125	282	391	444	467
AB Duration	12 weeks	25	43	51	55	56
AB Duration	6 weeks	25	64	94	109	116

Table 6.2: Expected number of participants entering into randomised comparisons

		Expected sample size for randomised comparisons by enrolment				
Domain	Treatment arm	500	1000	1500	2000	2500
AB Ext-proph	6 weeks	70	122	145	153	156
AB Ext-proph	12 weeks	70	176	260	305	326
AB Choice	No-rif	150	234	262	271	274
AB Choice	Rif	150	353	514	603	648
RD = -0.05: abx duration 6wk effect +silo specific d1						
Surgical	DAIR	125	303	474	628	766
Surgical	rev(1)	37	56	68	76	83
Surgical	rev(2)	87	130	158	178	194
Surgical	Revision	125	185	226	255	276
AB Duration	12 weeks	25	45	61	75	86
AB Duration	6 weeks	25	41	54	64	73
AB Ext-proph	6 weeks	70	142	204	256	300
AB Ext-proph	12 weeks	70	94	109	120	129
AB Choice	No-rif	150	382	609	814	996
AB Choice	Rif	150	204	230	245	255
RD = 0.12 surgical, RD = 0.08 abx choice +silo specific d1						
Surgical	DAIR	125	217	278	319	347
Surgical	rev(1)	38	83	128	166	198
Surgical	rev(2)	87	193	298	387	460
Surgical	Revision	125	276	425	553	658
AB Duration	12 weeks	25	52	77	98	115
AB Duration	6 weeks	25	54	81	103	121
AB Ext-proph	6 weeks	70	187	307	411	498
AB Ext-proph	12 weeks	70	108	133	150	162
AB Choice	No-rif	150	232	261	272	279
AB Choice	Rif	150	361	584	774	928

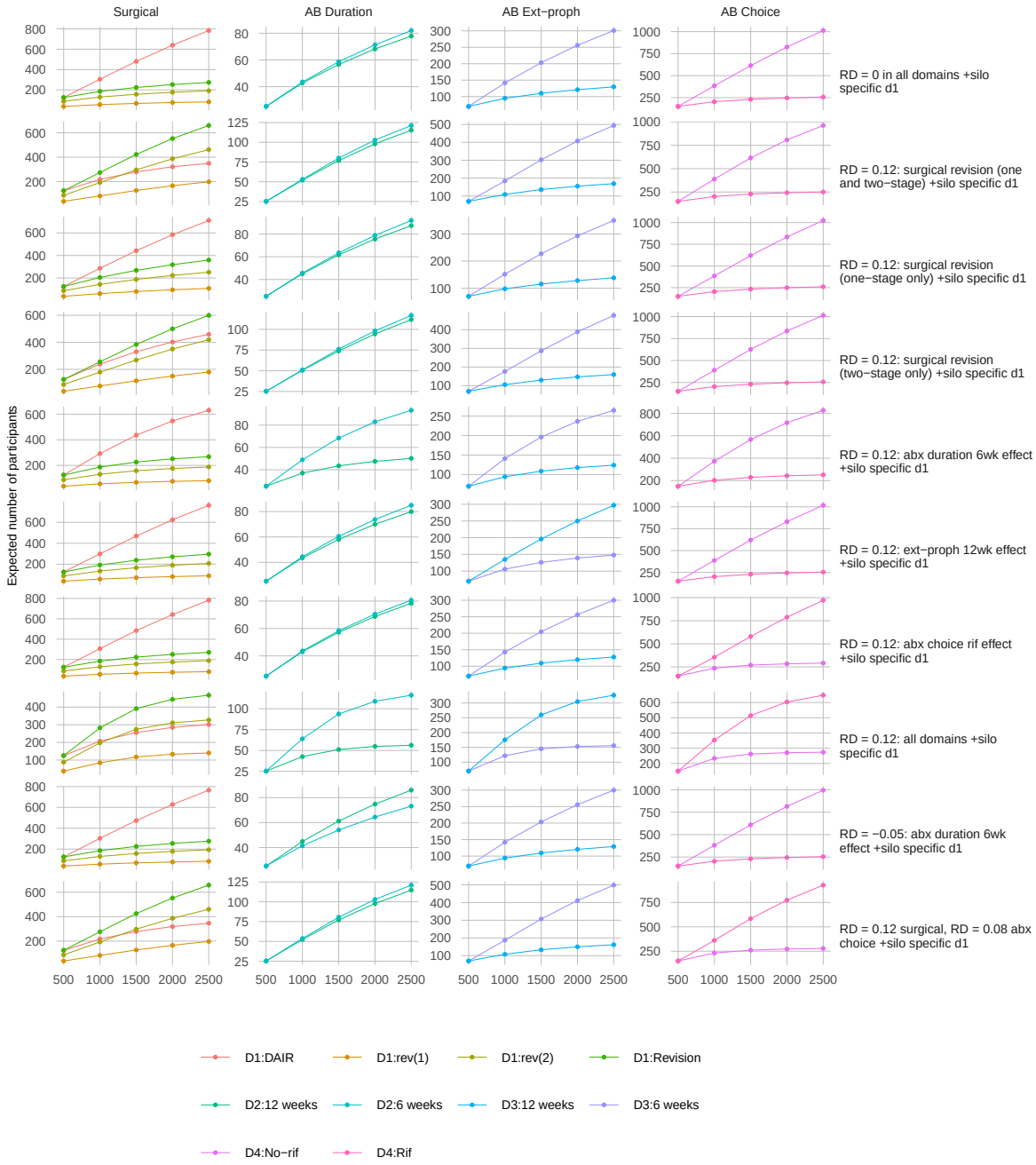

Figure 6.1: Expected number of participants entering into randomised comparisons

6.2.2 Expected sample size

Table 6.3 shows the expected sample size at which each decision is made by domain and scenario and, in parentheses, the proportion of trials on which the decision type was made.

Table 6.3: Expected number of enrolments by decision type (including reaching maximum sample size)

	Expected number of total enrolments to hit stopping rule by domain			
Decision	Surgical	AB Duration	AB Ext-proph	AB choice
RD = 0 in all domains +silo specific d1				
superiority	1,220 (7%)		1,061 (9%)	1,137 (3%)
futility (sup)	839 (86%)		811 (82%)	766 (96%)
ni		1,208 (31%)		
futility (ni)		1,101 (20%)		
-	2,500 (7%)	2,500 (49%)	2,500 (9%)	2,500 (1%)
RD = 0.12: surgical revision (one and two-stage) +silo specific d1				
superiority	1,085 (84%)		1,035 (10%)	1,127 (2%)
futility (sup)	775 (10%)		823 (88%)	757 (96%)
ni		1,300 (39%)		
futility (ni)		1,135 (23%)		
-	2,500 (6%)	2,500 (38%)	2,500 (3%)	2,500 (1%)
RD = 0.12: surgical revision (one-stage only) +silo specific d1				
superiority	1,315 (16%)		1,092 (9%)	1,141 (3%)
futility (sup)	924 (70%)		821 (83%)	767 (95%)
ni		1,212 (32%)		
futility (ni)		1,090 (21%)		
-	2,500 (13%)	2,500 (47%)	2,500 (8%)	2,500 (2%)
RD = 0.12: surgical revision (two-stage only) +silo specific d1				
superiority	1,221 (66%)		1,055 (9%)	1,100 (3%)
futility (sup)	866 (22%)		832 (88%)	761 (96%)
ni		1,308 (35%)		
futility (ni)		1,117 (22%)		
-	2,500 (12%)	2,500 (42%)	2,500 (3%)	2,500 (2%)
RD = 0.12: abx duration 6wk effect +silo specific d1				
superiority	1,245 (7%)		1,047 (9%)	1,203 (3%)
futility (sup)	865 (86%)		813 (83%)	761 (96%)

Table 6.3: Expected number of enrolments by decision type (including reaching maximum sample size)

	Expected number of total enrolments to hit stopping rule by domain			
Decision	Surgical	AB Duration	AB Ext-proph	AB choice
ni		1,041 (85%)		
futility (ni)		771 (2%)		
-	2,500 (7%)	2,500 (13%)	2,500 (8%)	2,500 (2%)
RD = 0.12: ext-proph 12wk effect +silo specific d1				
superiority	1,177 (8%)		976 (82%)	1,200 (3%)
futility (sup)	884 (83%)		718 (12%)	754 (96%)
ni		1,186 (32%)		
futility (ni)		1,099 (20%)		
-	2,500 (9%)	2,500 (48%)	2,500 (6%)	2,500 (1%)
RD = 0.12: abx choice rif effect +silo specific d1				
superiority	1,244 (6%)		1,032 (9%)	862 (96%)
futility (sup)	840 (87%)		817 (83%)	571 (4%)
ni		1,225 (31%)		
futility (ni)		1,094 (21%)		
-	2,500 (7%)	2,500 (48%)	2,500 (8%)	2,500 (0%)
RD = 0.12: all domains +silo specific d1				
superiority	1,019 (87%)		881 (90%)	849 (96%)
futility (sup)	850 (8%)		640 (9%)	603 (4%)
ni		970 (97%)		
futility (ni)		670 (1%)		
-	2,500 (5%)	2,500 (2%)	2,500 (0%)	2,500 (0%)
RD = -0.05: abx duration 6wk effect +silo specific d1				
superiority	1,254 (6%)		1,091 (8%)	1,136 (2%)
futility (sup)	848 (86%)		824 (83%)	762 (96%)
ni		1,094 (14%)		
futility (ni)		1,143 (41%)		
-	2,500 (8%)	2,500 (45%)	2,500 (8%)	2,500 (1%)
RD = 0.12 surgical, RD = 0.08 abx choice +silo specific d1				
superiority	1,074 (83%)		1,032 (9%)	838 (96%)
futility (sup)	815 (11%)		812 (89%)	571 (4%)
ni		1,318 (40%)		
futility (ni)		1,120 (22%)		

Table 6.3: Expected number of enrolments by decision type (including reaching maximum sample size)

	Expected number of total enrolments to hit stopping rule by domain			
Decision	Surgical	AB Duration	AB Ext-proph	AB choice
-	2,500 (6%)	2,500 (38%)	2,500 (2%)	2,500 (0%)

6.3 Parameter estimation

Table 6.4 and Figure 6.2 show the expected value of the posterior means for the treatment effects by domain and interim analyse under each scenario along with the 95% interval of the posterior means.

Table 6.4: Parameter estimation - risk difference (expectation of posterior means and 95% interval)

	Risk difference (expectation of posterior means and 95 pct interval)				
Domain	500	1000	1500	2000	2500
RD = 0 in all domains +silo specific d1					
Surgical	0 (-0.14, 0.14)	0 (-0.12, 0.11)	-0.01 (-0.12, 0.1)	-0.01 (-0.11, 0.1)	-0.01 (-0.11, 0.1)
AB Duration	0 (-0.22, 0.22)	0 (-0.21, 0.2)	0 (-0.2, 0.2)	0 (-0.2, 0.2)	0 (-0.2, 0.2)
AB Ext-proph	0 (-0.16, 0.16)	0 (-0.13, 0.13)	0 (-0.13, 0.13)	0 (-0.13, 0.12)	-0.01 (-0.13, 0.12)
AB Choice	0 (-0.11, 0.11)	0 (-0.09, 0.08)	0 (-0.08, 0.07)	0 (-0.08, 0.06)	0 (-0.08, 0.06)
RD = 0.12: surgical revision (one and two-stage) +silo specific d1					
Surgical	0.11 (-0.03, 0.24)	0.11 (-0.01, 0.23)	0.12 (0, 0.22)	0.12 (0, 0.22)	0.12 (0, 0.22)
AB Duration	0 (-0.21, 0.21)	0 (-0.19, 0.19)	0 (-0.18, 0.19)	0 (-0.18, 0.18)	0 (-0.18, 0.18)
AB Ext-proph	0 (-0.15, 0.15)	0 (-0.13, 0.12)	0 (-0.12, 0.11)	-0.01 (-0.12, 0.11)	-0.01 (-0.12, 0.11)
AB Choice	0 (-0.1, 0.1)	0 (-0.08, 0.08)	0 (-0.08, 0.07)	0 (-0.08, 0.06)	0 (-0.08, 0.06)
RD = 0.12: surgical revision (one-stage only) +silo specific d1					
Surgical	0.02 (-0.12, 0.16)	0.02 (-0.1, 0.14)	0.02 (-0.09, 0.13)	0.02 (-0.09, 0.13)	0.02 (-0.09, 0.13)
AB Duration	0 (-0.22, 0.22)	0 (-0.2, 0.2)	0 (-0.19, 0.19)	0 (-0.19, 0.19)	0 (-0.19, 0.19)
AB Ext-proph	0 (-0.16, 0.15)	0 (-0.13, 0.13)	0 (-0.13, 0.12)	-0.01 (-0.13, 0.12)	-0.01 (-0.12, 0.11)
AB Choice	0 (-0.11, 0.11)	0 (-0.08, 0.08)	0 (-0.08, 0.07)	0 (-0.08, 0.06)	0 (-0.08, 0.06)
RD = 0.12: surgical revision (two-stage only) +silo specific d1					
Surgical	0.08 (-0.06, 0.22)	0.09 (-0.03, 0.2)	0.09 (-0.03, 0.2)	0.09 (-0.02, 0.2)	0.09 (-0.02, 0.2)

Table 6.4: Parameter estimation - risk difference (expectation of posterior means and 95% interval)

	Risk difference (expectation of posterior means and 95 pct interval)				
Domain	500	1000	1500	2000	2500
AB Duration	0 (-0.22, 0.22)	0 (-0.2, 0.2)	0 (-0.19, 0.19)	0 (-0.19, 0.19)	0 (-0.19, 0.19)
AB Ext-proph	0 (-0.15, 0.15)	0 (-0.13, 0.12)	0 (-0.12, 0.11)	-0.01 (-0.12, 0.1)	-0.01 (-0.11, 0.1)
AB Choice	0 (-0.11, 0.11)	0 (-0.09, 0.08)	0 (-0.08, 0.07)	0 (-0.08, 0.06)	0 (-0.08, 0.06)
RD = 0.12: abx duration 6wk effect +silo specific d1					
Surgical	0 (-0.14, 0.14)	0 (-0.13, 0.12)	-0.01 (-0.12, 0.11)	-0.01 (-0.12, 0.11)	-0.01 (-0.12, 0.11)
AB Duration	0.1 (-0.12, 0.31)	0.11 (-0.08, 0.3)	0.12 (-0.06, 0.3)	0.12 (-0.04, 0.3)	0.13 (-0.03, 0.3)
AB Ext-proph	0 (-0.15, 0.16)	0 (-0.14, 0.13)	0 (-0.13, 0.13)	-0.01 (-0.13, 0.13)	-0.01 (-0.13, 0.13)
AB Choice	0 (-0.11, 0.11)	0 (-0.09, 0.08)	0 (-0.09, 0.07)	0 (-0.08, 0.06)	0 (-0.08, 0.06)
RD = 0.12: ext-proph 12wk effect +silo specific d1					
Surgical	0.01 (-0.13, 0.15)	0 (-0.11, 0.12)	0 (-0.11, 0.11)	0 (-0.11, 0.11)	0 (-0.11, 0.1)
AB Duration	0 (-0.22, 0.22)	0 (-0.2, 0.2)	0 (-0.19, 0.2)	0 (-0.19, 0.19)	0 (-0.19, 0.19)
AB Ext-proph	0.11 (-0.04, 0.26)	0.12 (-0.02, 0.24)	0.12 (-0.01, 0.24)	0.12 (-0.01, 0.24)	0.12 (-0.01, 0.24)
AB Choice	0 (-0.11, 0.11)	0 (-0.09, 0.08)	0 (-0.08, 0.07)	0 (-0.08, 0.06)	0 (-0.08, 0.06)
RD = 0.12: abx choice rif effect +silo specific d1					
Surgical	0 (-0.14, 0.13)	0 (-0.12, 0.11)	-0.01 (-0.12, 0.1)	-0.01 (-0.11, 0.09)	-0.01 (-0.11, 0.09)
AB Duration	0 (-0.22, 0.22)	0 (-0.2, 0.2)	0 (-0.19, 0.19)	0 (-0.19, 0.19)	0 (-0.19, 0.19)
AB Ext-proph	0 (-0.16, 0.15)	0 (-0.13, 0.13)	0 (-0.13, 0.12)	0 (-0.12, 0.12)	-0.01 (-0.12, 0.12)
AB Choice	0.12 (0.01, 0.22)	0.12 (0.04, 0.2)	0.12 (0.05, 0.2)	0.12 (0.05, 0.2)	0.12 (0.06, 0.2)
RD = 0.12: all domains +silo specific d1					
Surgical	0.12 (-0.01, 0.24)	0.12 (0, 0.23)	0.12 (0.01, 0.22)	0.12 (0.01, 0.22)	0.12 (0.01, 0.22)
AB Duration	0.1 (-0.09, 0.29)	0.11 (-0.04, 0.28)	0.12 (-0.01, 0.28)	0.12 (0, 0.28)	0.13 (0.01, 0.28)
AB Ext-proph	0.11 (-0.02, 0.25)	0.12 (0, 0.23)	0.12 (0.01, 0.23)	0.12 (0.01, 0.23)	0.12 (0.01, 0.23)
AB Choice	0.12 (0.02, 0.22)	0.12 (0.04, 0.2)	0.12 (0.05, 0.19)	0.12 (0.05, 0.19)	0.12 (0.05, 0.19)
RD = -0.05: abx duration 6wk effect +silo specific d1					
Surgical	0 (-0.14, 0.14)	0 (-0.12, 0.11)	-0.01 (-0.12, 0.1)	-0.01 (-0.11, 0.1)	-0.01 (-0.11, 0.1)
AB Duration	-0.04 (-0.26, 0.18)	-0.05 (-0.25, 0.16)	-0.05 (-0.24, 0.16)	-0.05 (-0.24, 0.16)	-0.05 (-0.24, 0.16)
AB Ext-proph	0 (-0.15, 0.15)	0 (-0.13, 0.13)	0 (-0.13, 0.12)	-0.01 (-0.13, 0.12)	-0.01 (-0.13, 0.12)
AB Choice	0 (-0.11, 0.11)	0 (-0.09, 0.08)	0 (-0.08, 0.07)	0 (-0.08, 0.06)	0 (-0.08, 0.06)
RD = 0.12 surgical, RD = 0.08 abx choice +silo specific d1					
Surgical	0.11 (-0.03, 0.24)	0.11 (0, 0.22)	0.11 (0, 0.22)	0.11 (0, 0.22)	0.12 (0.01, 0.21)
AB Duration	0 (-0.2, 0.2)	0 (-0.18, 0.18)	0 (-0.17, 0.17)	0 (-0.17, 0.17)	0 (-0.17, 0.17)

Table 6.4: Parameter estimation - risk difference (expectation of posterior means and 95% interval)

	Risk difference (expectation of posterior means and 95 pct interval)				
Domain	500	1000	1500	2000	2500
AB Ext-proph	0 (-0.15, 0.14)	0 (-0.12, 0.11)	-0.01 (-0.11, 0.1)	-0.01 (-0.11, 0.1)	-0.01 (-0.11, 0.1)
AB Choice	0.12 (0.02, 0.22)	0.12 (0.04, 0.2)	0.12 (0.05, 0.2)	0.12 (0.06, 0.2)	0.12 (0.06, 0.2)

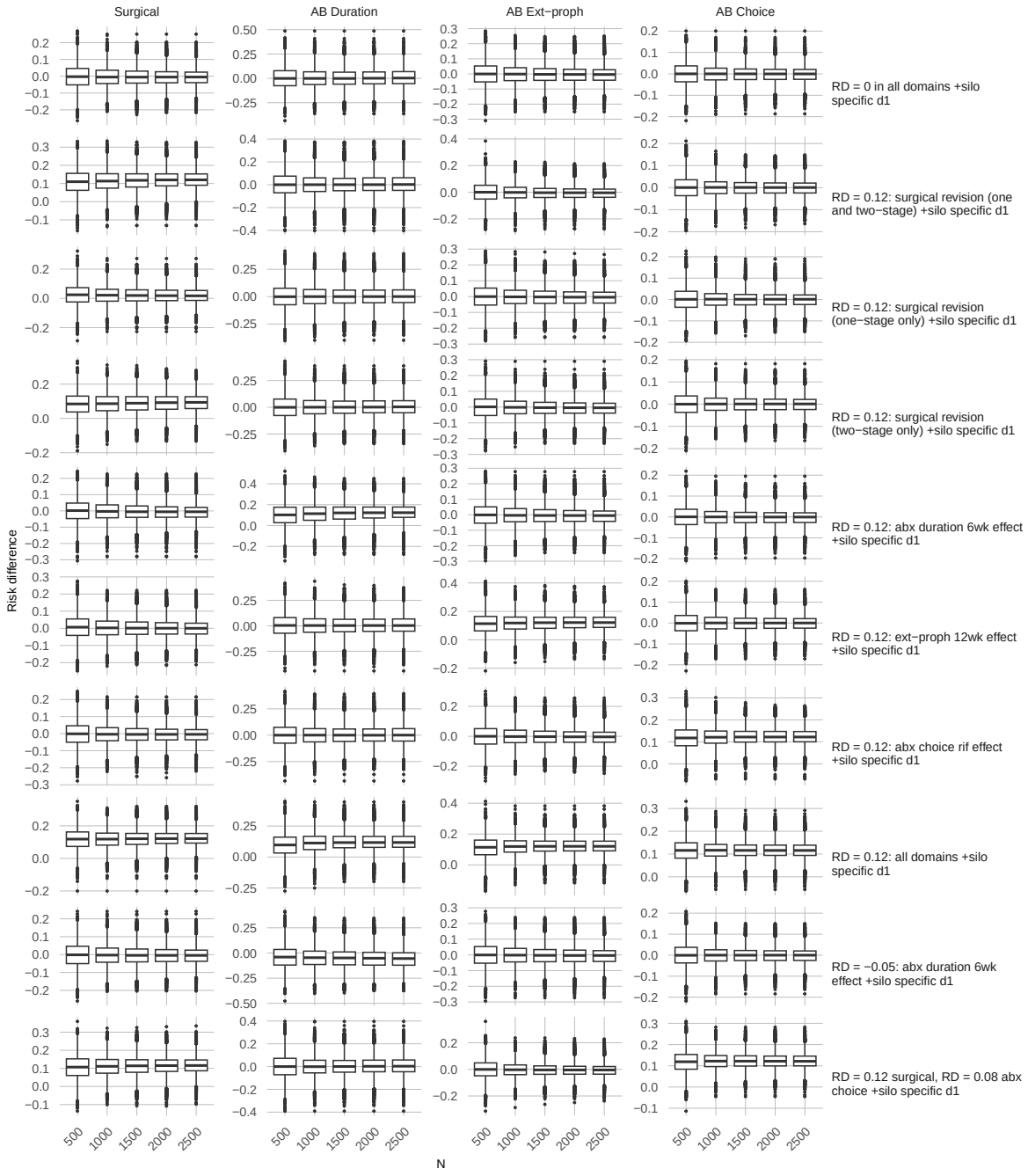

Figure 6.2: Expectation of posterior means for risk difference treatment effects by domain and simulation scenario

6.4 Observed proportion with treatment success

Table 6.5 shows the observed proportion with treatment success by domain and treatment arm. For simplicity, the treatment arms have been represented generically by the numbers 1 to 3 and have a domain specific interpretation.

For the surgical domain, 1 corresponds to DAIR, 2 corresponds to one-stage revision and 3 corresponds to two-stage revision. For the antibiotic duration domain, 2 corresponds to 12 weeks and 3 corresponds to 6 weeks. For the extended prophylaxis domain, 2 corresponds to 6 weeks and 3 corresponds to 12 weeks. For the antibiotic choice domain, 2 corresponds to no rifampacin and 3 corresponds to rifampacin.

Table 6.5: Observed proportion with treatment success

Empirical risk by domain and treatment arm			
Domain	1	2	3
RD = 0 in all domains +silo specific d1			
Surgical	0.59	0.62	0.57
AB Duration	-	0.65	0.65
AB Ext-proph	-	0.6	0.6
AB Choice	-	0.62	0.62
RD = 0.12: surgical revision (one and two-stage) +silo specific d1			
Surgical	0.56	0.71	0.67
AB Duration	-	0.7	0.7
AB Ext-proph	-	0.65	0.65
AB Choice	-	0.64	0.64
RD = 0.12: surgical revision (one-stage only) +silo specific d1			
Surgical	0.56	0.68	0.55
AB Duration	-	0.68	0.68
AB Ext-proph	-	0.59	0.59
AB Choice	-	0.61	0.61
RD = 0.12: surgical revision (two-stage only) +silo specific d1			
Surgical	0.56	0.6	0.68
AB Duration	-	0.63	0.63
AB Ext-proph	-	0.66	0.66
AB Choice	-	0.63	0.63

Table 6.5: Observed proportion with treatment success

Empirical risk by domain and treatment arm			
Domain	1	2	3
RD = 0.12: abx duration 6wk effect +silo specific d1			
Surgical	0.59	0.66	0.57
AB Duration	-	0.63	0.75
AB Ext-proph	-	0.6	0.6
AB Choice	-	0.62	0.62
RD = 0.12: ext-proph 12wk effect +silo specific d1			
Surgical	0.58	0.62	0.62
AB Duration	-	0.65	0.65
AB Ext-proph	-	0.58	0.7
AB Choice	-	0.63	0.63
RD = 0.12: abx choice rif effect +silo specific d1			
Surgical	0.62	0.65	0.61
AB Duration	-	0.69	0.69
AB Ext-proph	-	0.63	0.63
AB Choice	-	0.6	0.72
RD = 0.12: all domains +silo specific d1			
Surgical	0.6	0.79	0.76
AB Duration	-	0.71	0.83
AB Ext-proph	-	0.66	0.78
AB Choice	-	0.64	0.76
RD = -0.05: abx duration 6wk effect +silo specific d1			
Surgical	0.59	0.62	0.57
AB Duration	-	0.67	0.62
AB Ext-proph	-	0.6	0.6
AB Choice	-	0.62	0.62
RD = 0.12 surgical, RD = 0.08 abx choice +silo specific d1			
Surgical	0.6	0.75	0.71
AB Duration	-	0.74	0.74
AB Ext-proph	-	0.69	0.69
AB Choice	-	0.62	0.74

6.5 References

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